US009175289B2

(12) **United States Patent**
Khvorova et al.

(10) **Patent No.: US 9,175,289 B2**
(45) **Date of Patent: *Nov. 3, 2015**

(54) **REDUCED SIZE SELF-DELIVERING RNAI COMPOUNDS**

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(*) Notice: Subject to any disclaimer, the term of this patent is extended or adjusted under 35 U.S.C. 154(b) by 0 days.

This patent is subject to a terminal disclaimer.

(21) Appl. No.: **14/278,900**

(22) Filed: **May 15, 2014**

(65) **Prior Publication Data**

US 2014/0364482 A1 Dec. 11, 2014

Related U.S. Application Data

(63) Continuation of application No. 13/120,342, filed as application No. PCT/US2009/005247 on Sep. 22, 2009, now Pat. No. 8,796,443.

(60) Provisional application No. 61/224,031, filed on Jul. 8, 2009, provisional application No. 61/149,946, filed on Feb. 4, 2009, provisional application No. 61/192,954, filed on Sep. 22, 2008.

(51) **Int. Cl.**

C12N 15/113	(2010.01)
C07H 21/04	(2006.01)
A61K 31/713	(2006.01)
C12N 15/11	(2006.01)

(52) **U.S. Cl.**

CPC ***C12N 15/113*** (2013.01); ***C12N 15/111*** (2013.01); *C12N 2310/315* (2013.01); *C12N 2310/321* (2013.01); *C12N 2310/322* (2013.01); *C12N 2310/3515* (2013.01); *C12N 2310/3519* (2013.01); *C12N 2320/32* (2013.01); *C12N 2320/51* (2013.01)

(58) **Field of Classification Search**

None

See application file for complete search history.

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(57) **ABSTRACT**

The present invention relates to RNAi constructs with minimal double-stranded regions, and their use in gene silencing. RNAi constructs associated with the invention include a double stranded region of 8-14 nucleotides and a variety of chemical modifications, and are highly effective in gene silencing.

17 Claims, 92 Drawing Sheets

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* cited by examiner

Figure 1

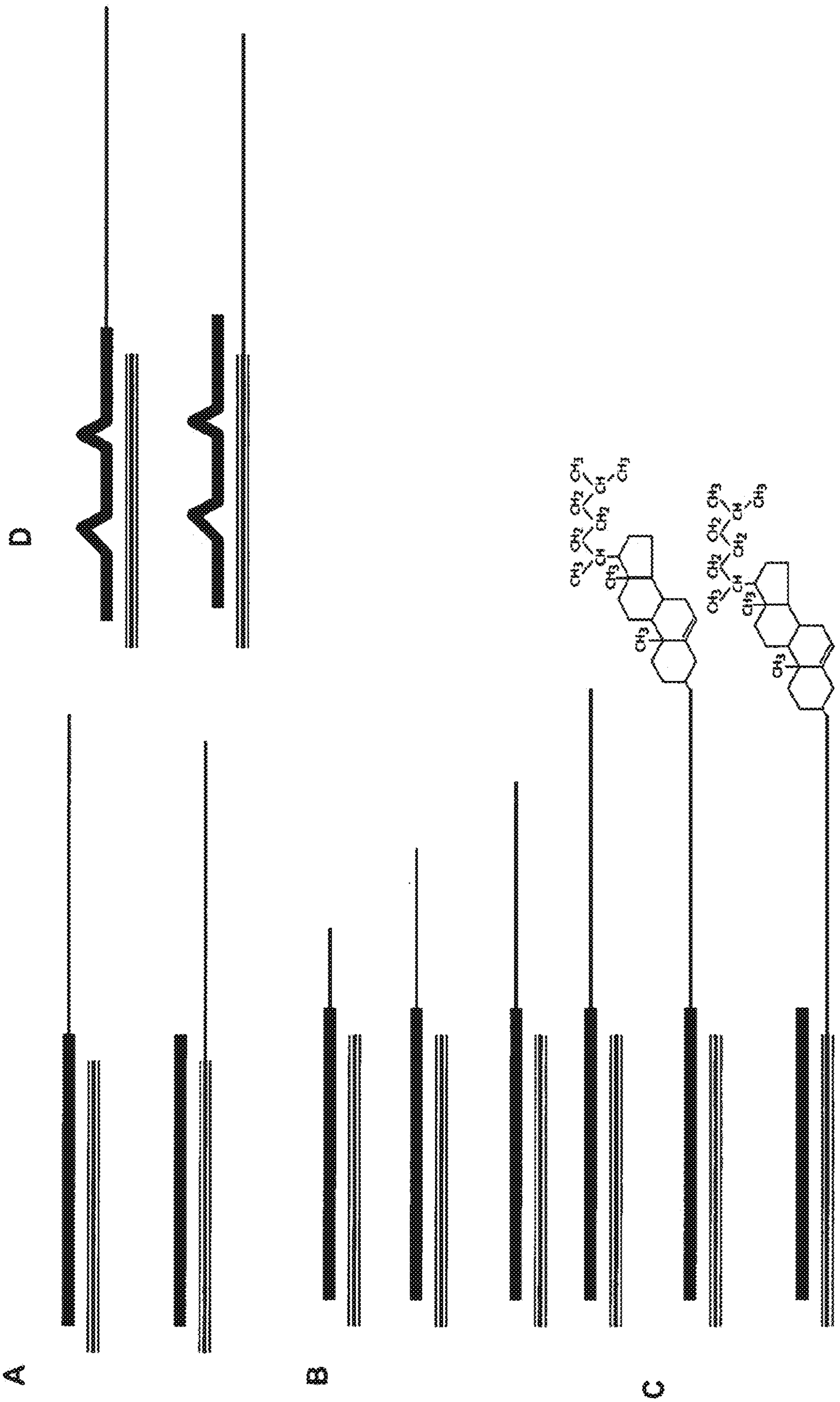
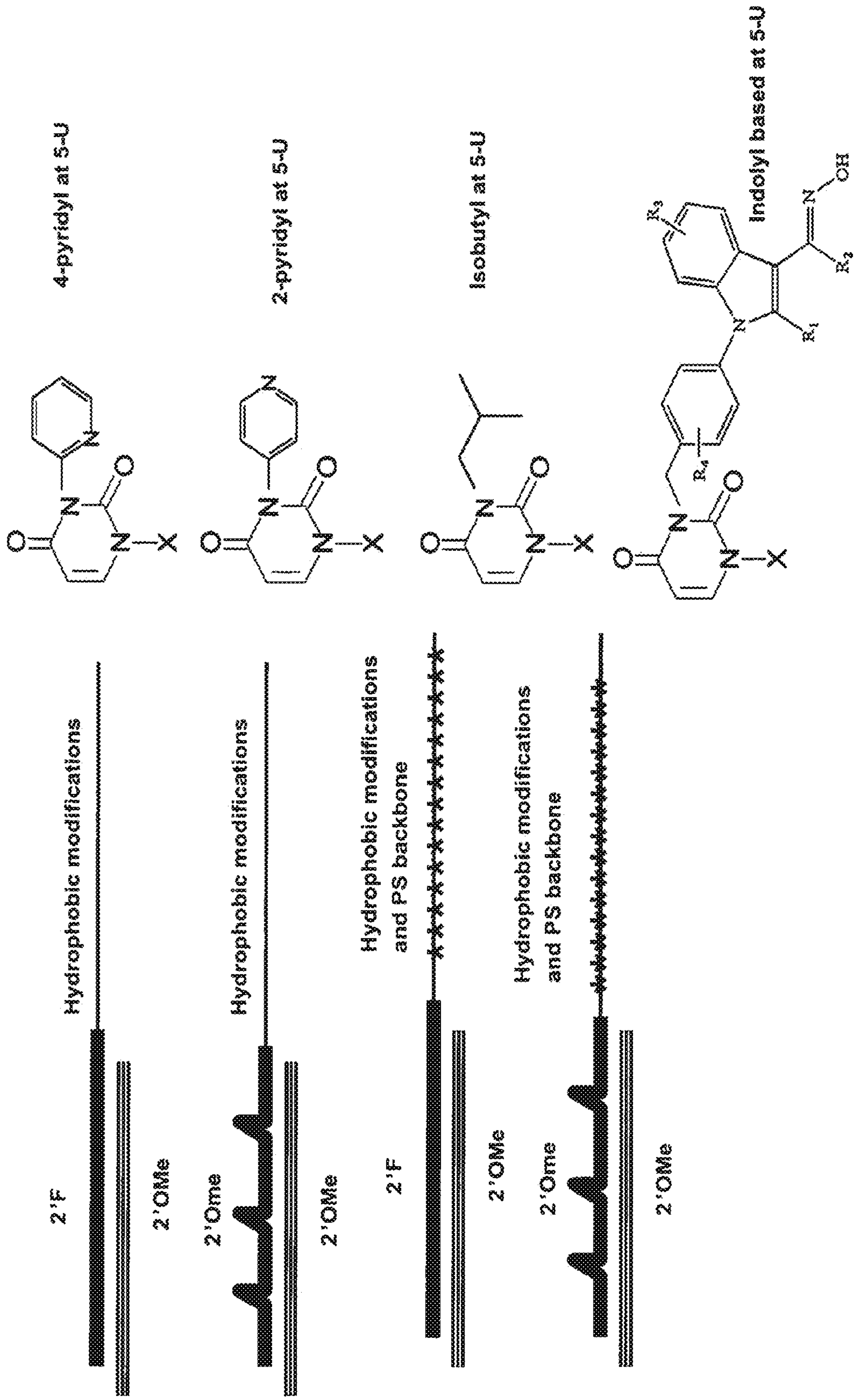


Figure 2



2'F
2'OMe
Hydrophobic modifications
2'Ome
2'OMe
Hydrophobic modifications
2'F
2'OMe
Hydrophobic modifications
and PS backbone
2'Ome
2'OMe
Hydrophobic modifications
and PS backbone
4-pyridyl at 5-U
2-pyridyl at 5-U
Isobutyl at 5-U
Indolyl based at 5-U

Figure 3

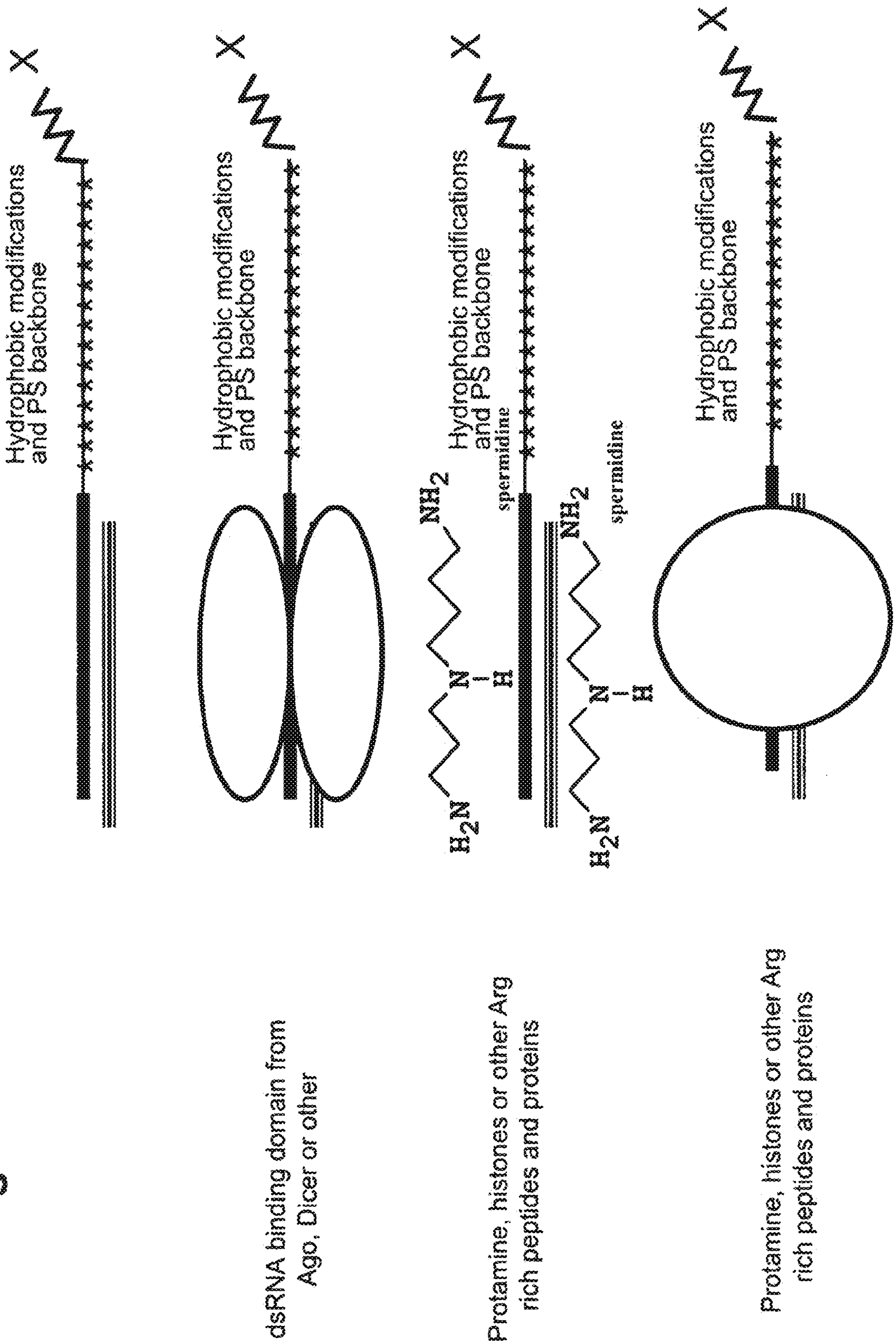
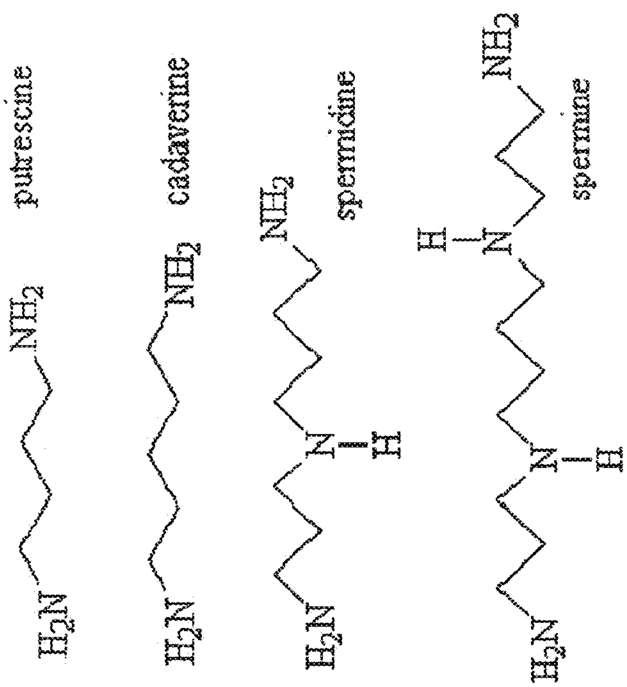

Hydrophobic modifications and PS backbone
dsRNA binding domain from Ago, Dicer or other
Hydrophobic modifications and PS backbone
Protamine, histones or other Arg rich peptides and proteins
Hydrophobic modifications and PS backbone
spermidine
spermidine
H_2N
N
H
NH_2
Protamine, histones or other Arg rich peptides and proteins
Hydrophobic modifications and PS backbone

Figure 4



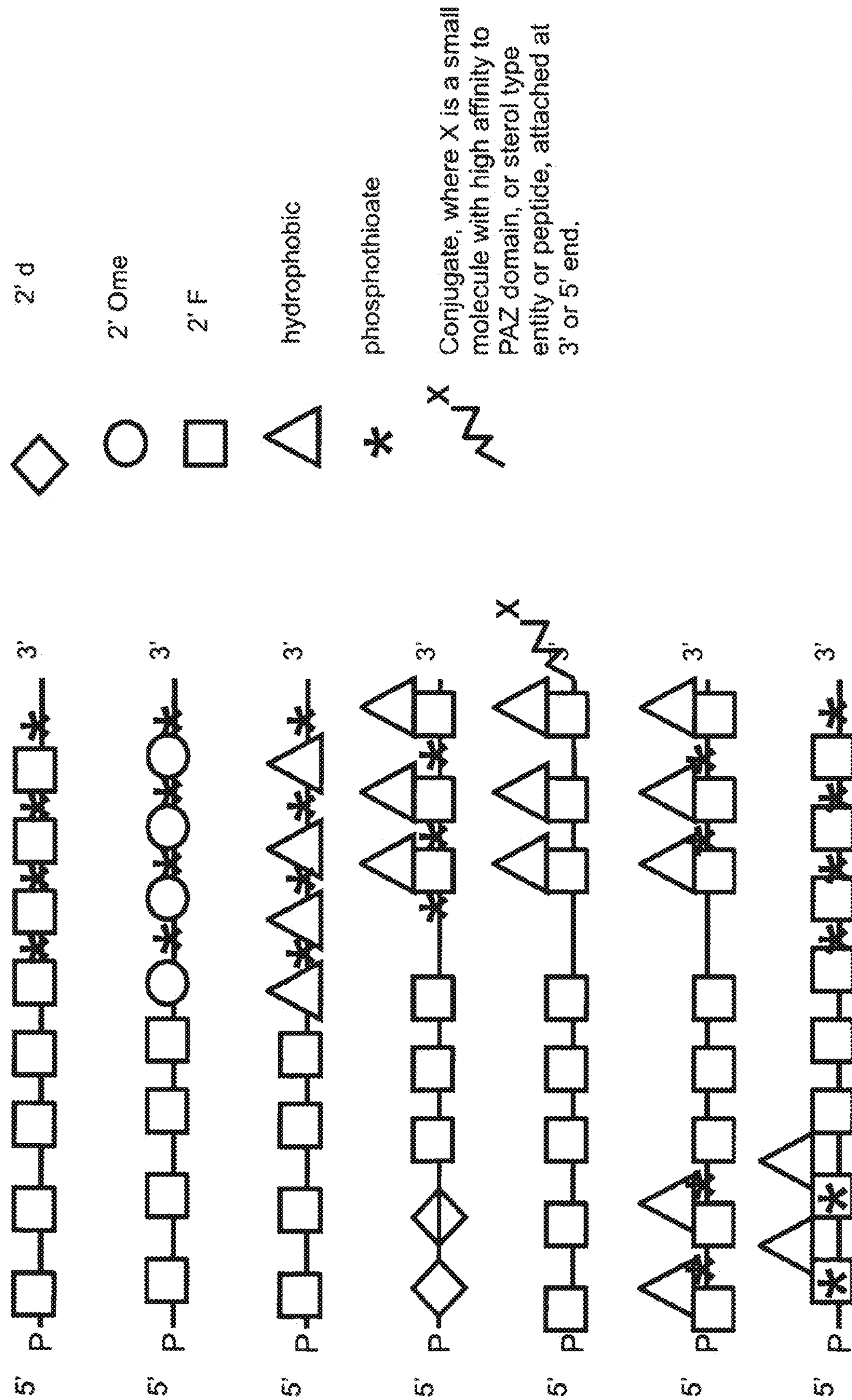

5'
P
3'
X
2' d
2' Ome
2' F
hydrophobic
phosphothioate
Conjugate, where X is a small molecule with high affinity to PAZ domain, or sterol type entity or peptide, attached at 3' or 5' end,

Figure 5

Figure 6

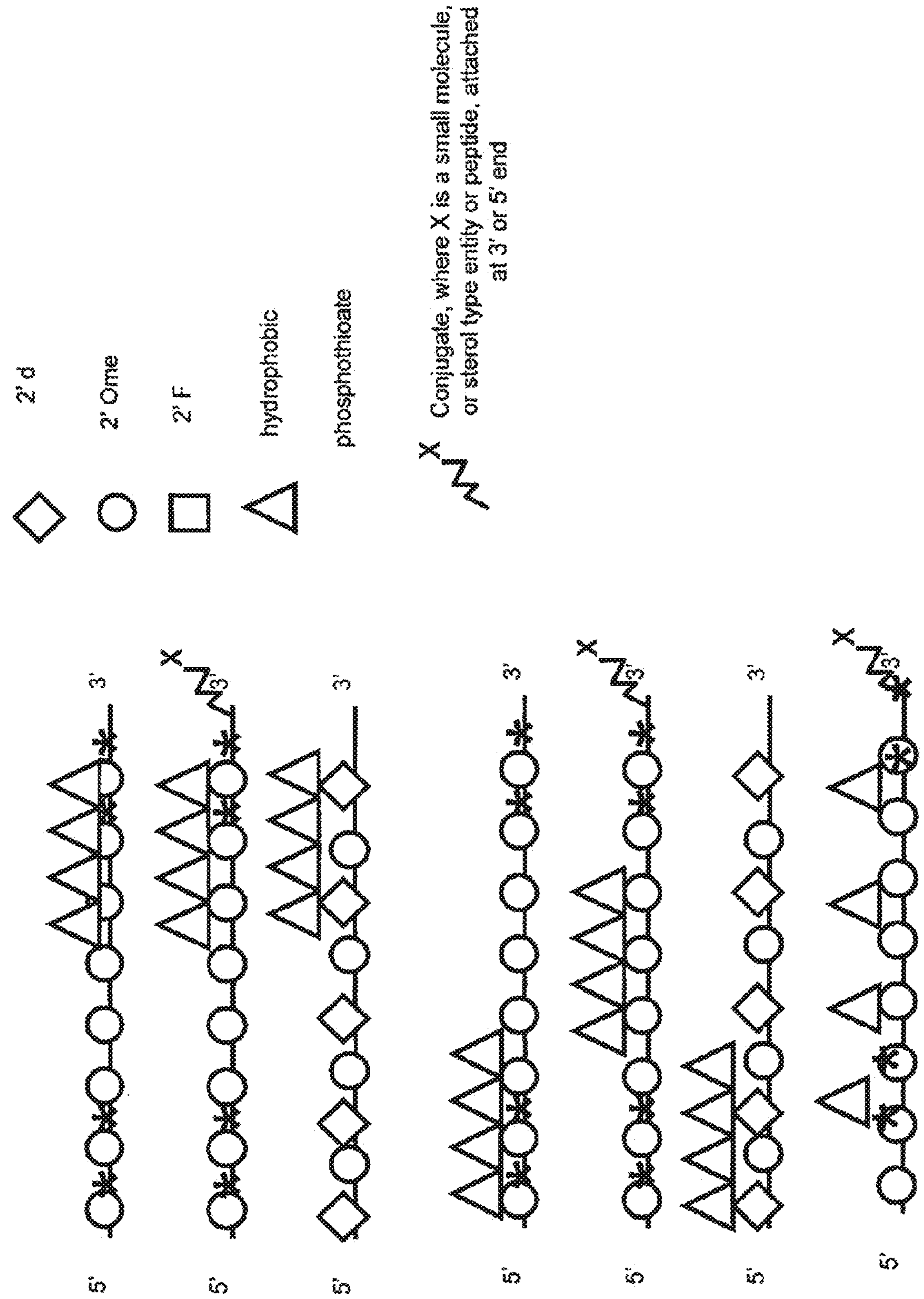

2' d
2' Ome
2' F
hydrophobic
phosphothioate
Conjugate, where X is a small molecule, or sterol type entity or peptide, attached at 3' or 5' end
5'
3'
X

Figure 7

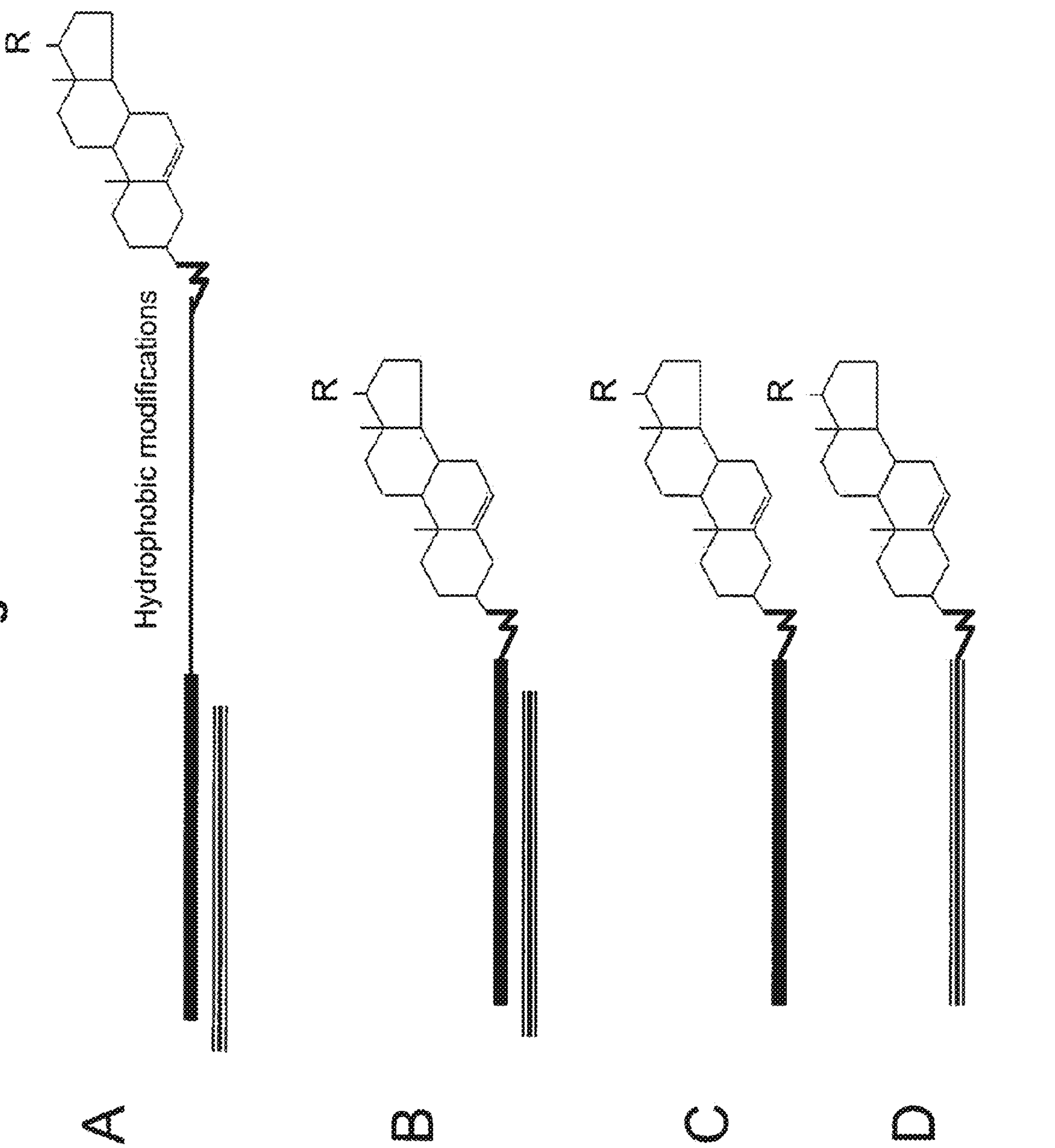
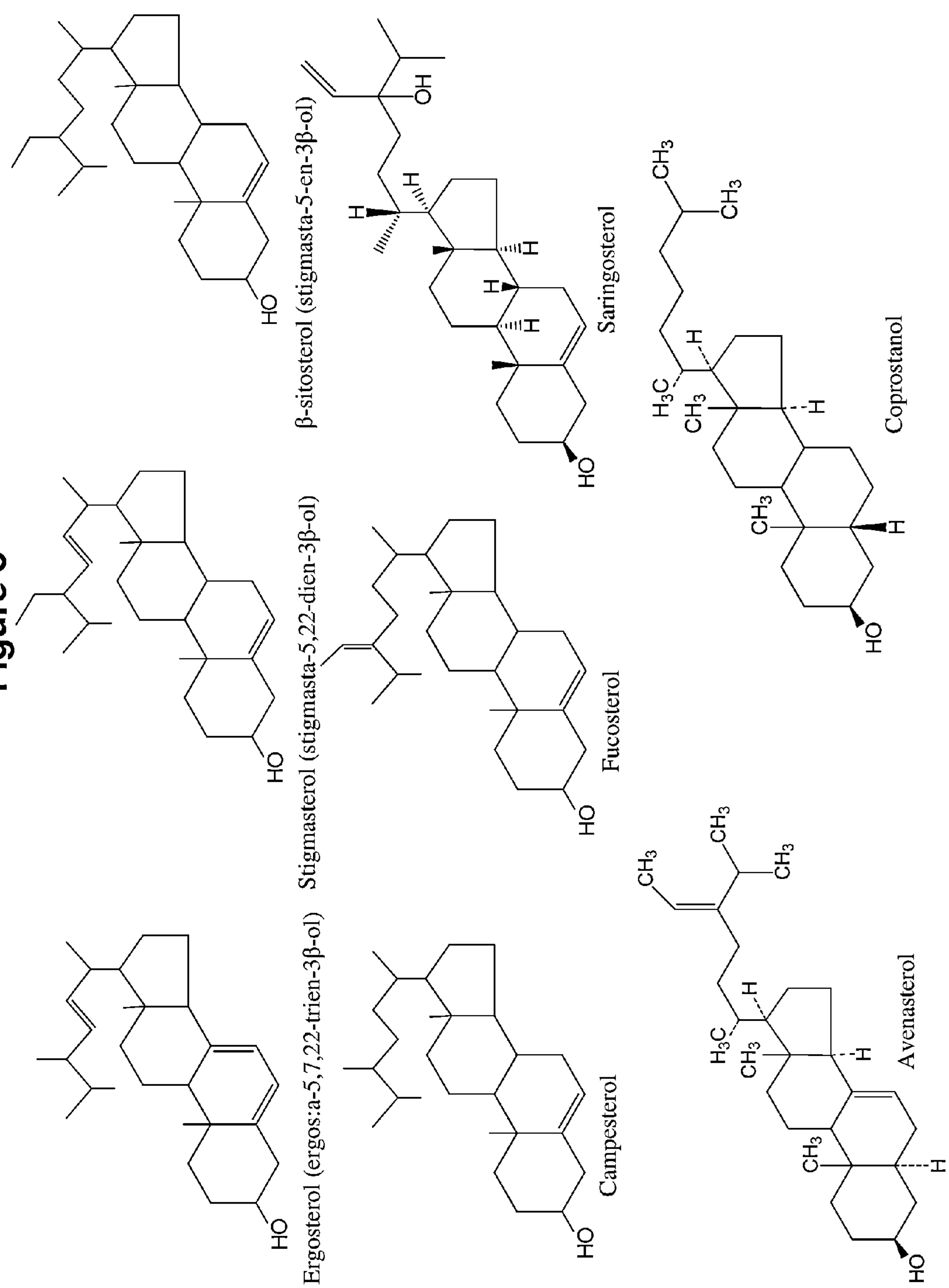


Figure 8



β-sitosterol (stigmasta-5-en-3β-ol)

Stigmasterol (stigmasta-5,22-dien-3β-ol)

Ergosterol (ergos:a-5,7,22-trien-3β-ol)

Saringosterol

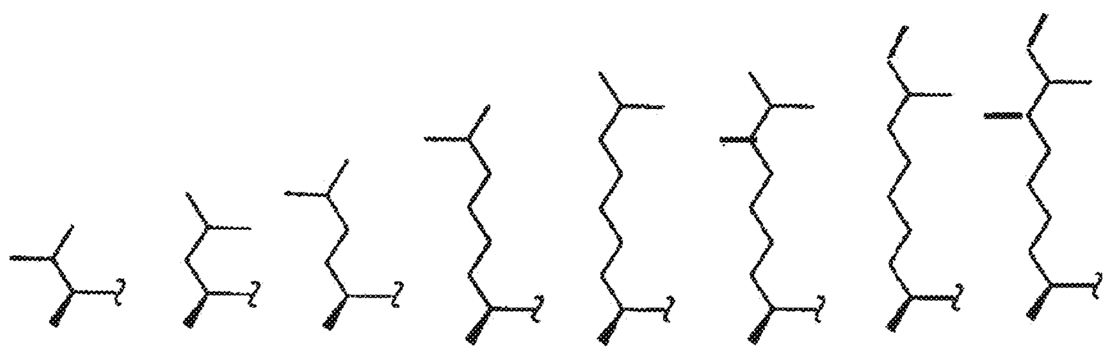
Fucosterol

Campesterol

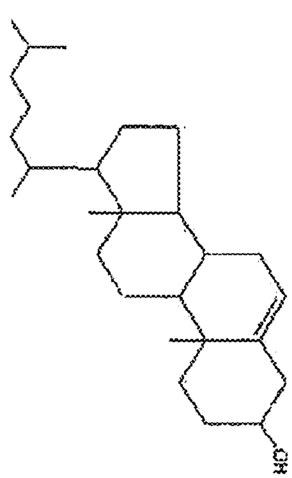
Coprostanol

Avenasterol

Figure 9



R-5 R-6 R-7 R-9 R-10 R-11a R-11b R-12



Cholesterol

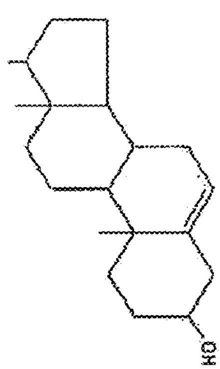
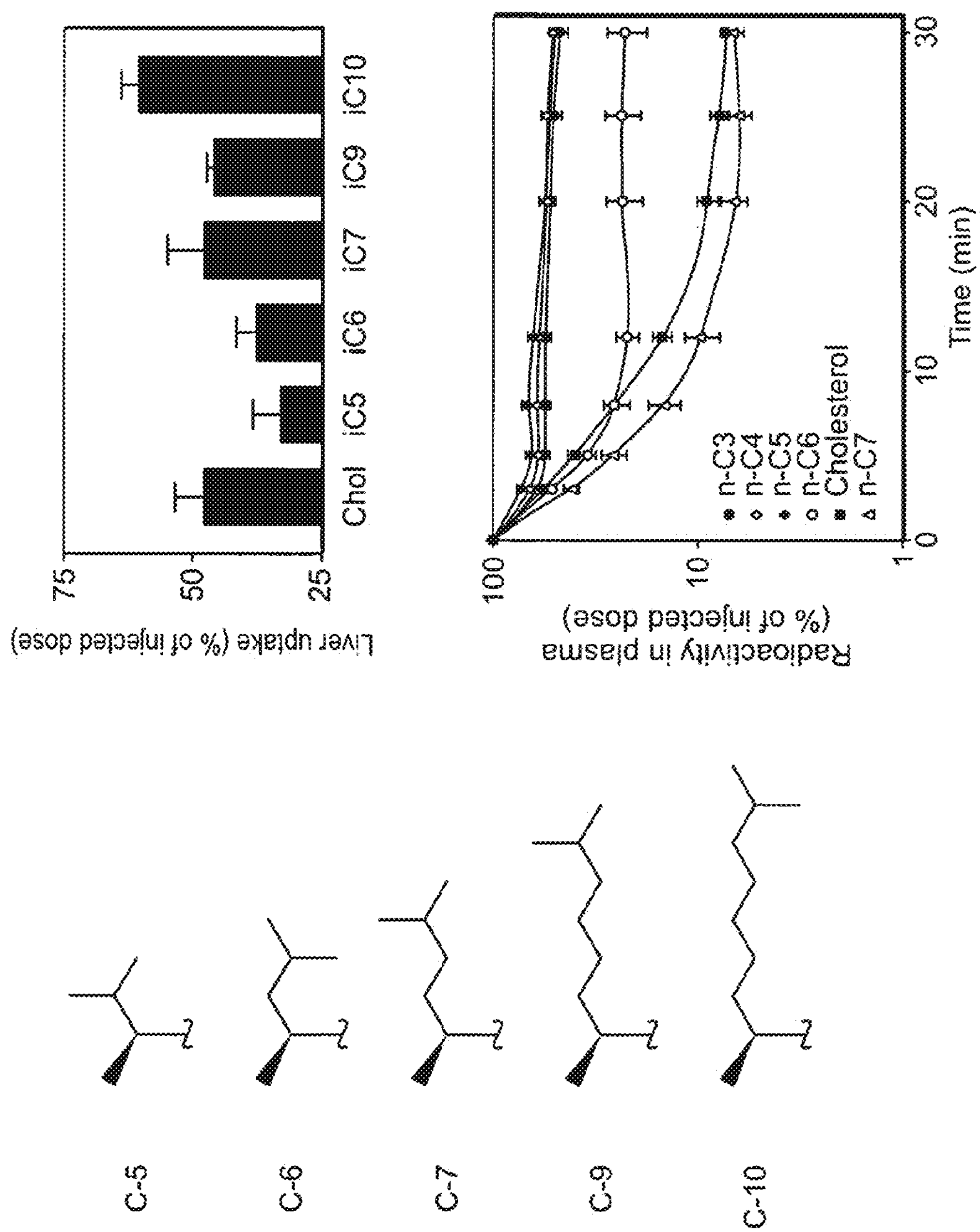
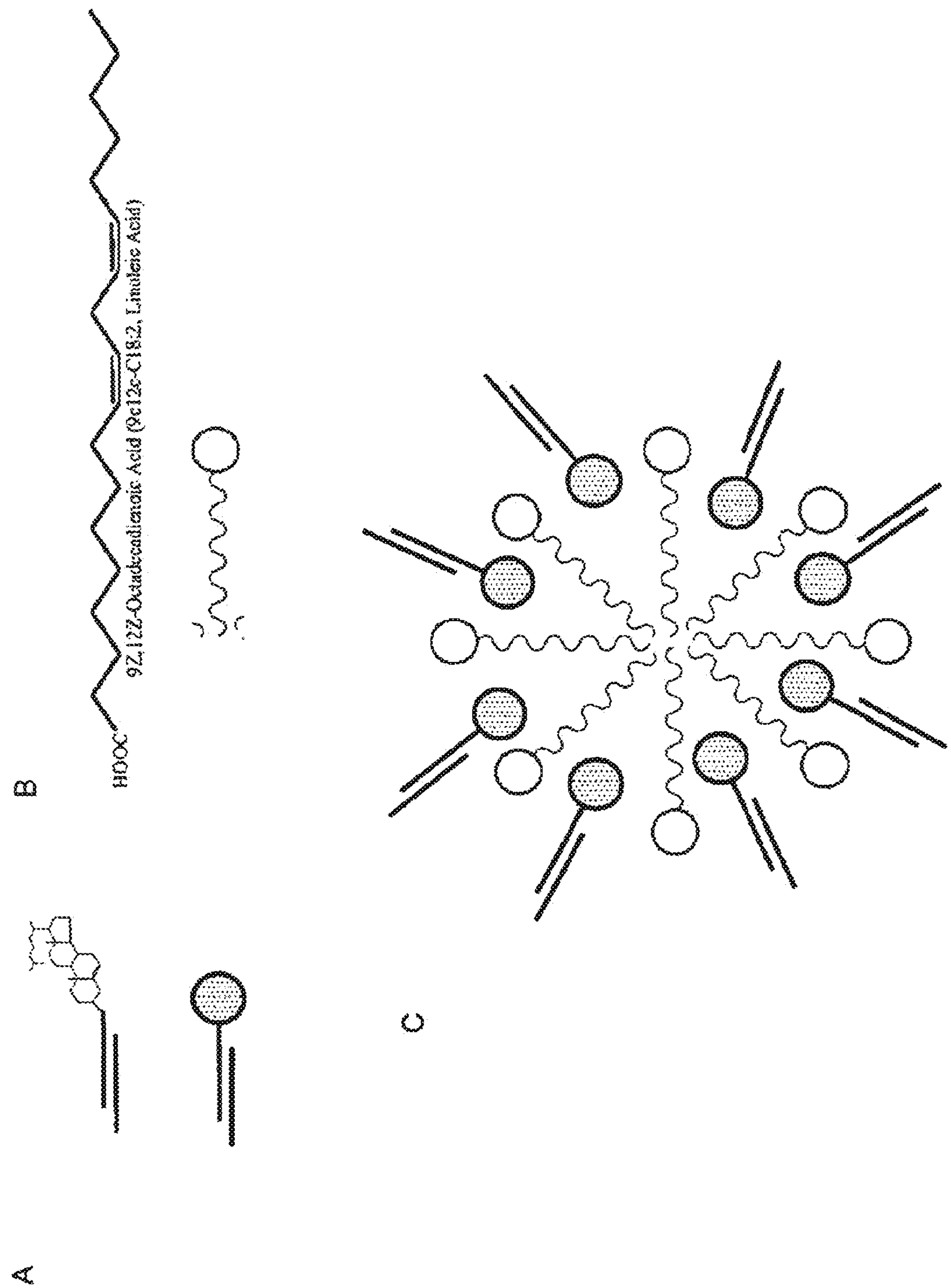


Figure 10



Liver uptake (% of injected dose)
75
50
25
Chol
iC5
iC6
iC7
iC9
iC10
Radioactivity in plasma
(% of injected dose)
100
10
1
0
10
20
30
Time (min)
n-C3
n-C4
n-C5
n-C6
Cholesterol
n-C7
C-5
C-6
C-7
C-9
C-10

Figure 11


A
B
HOOC
9Z,12Z-Octadecadienoic Acid (9c12c-C18:2, Linoleic Acid)
C

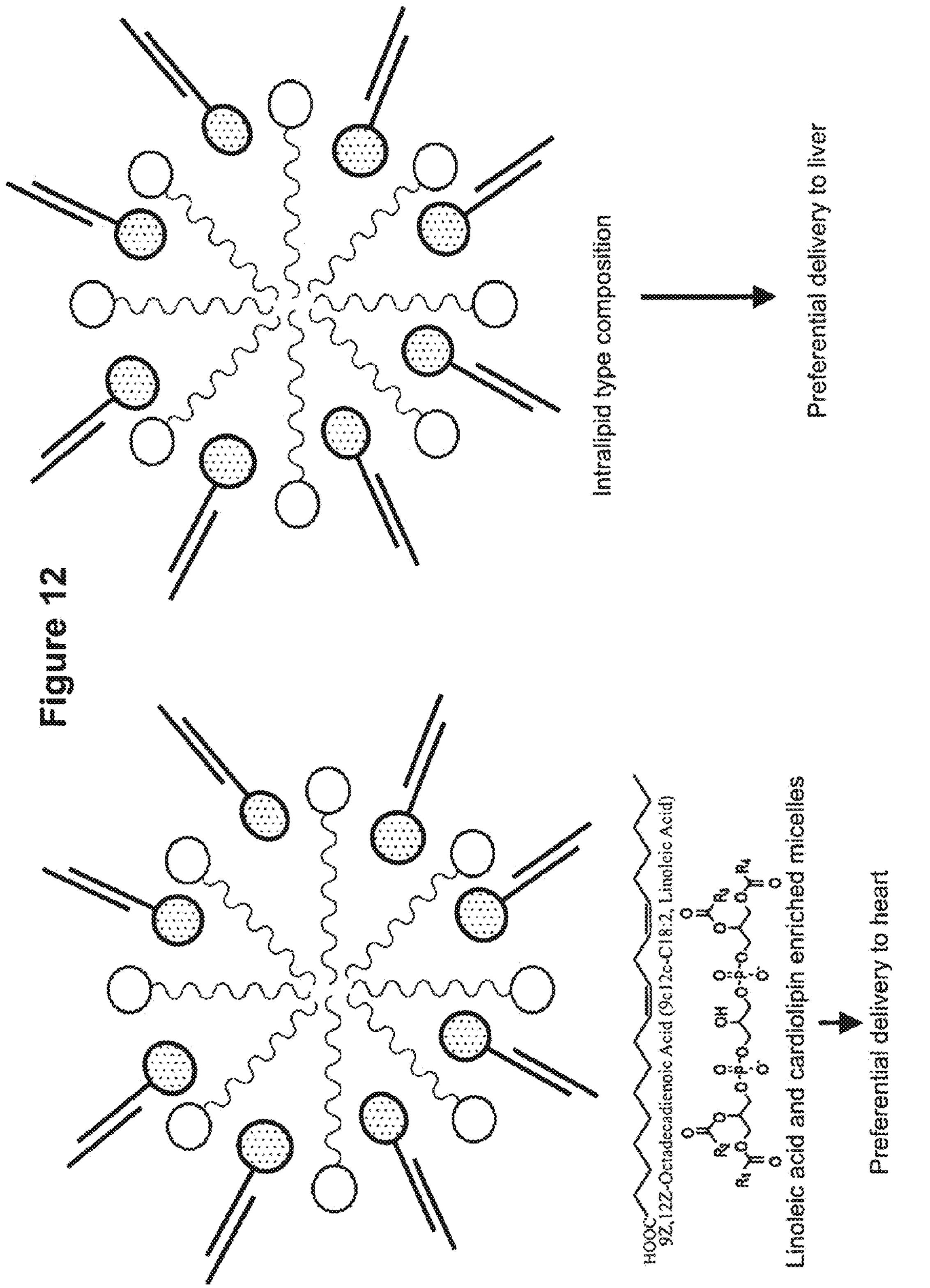
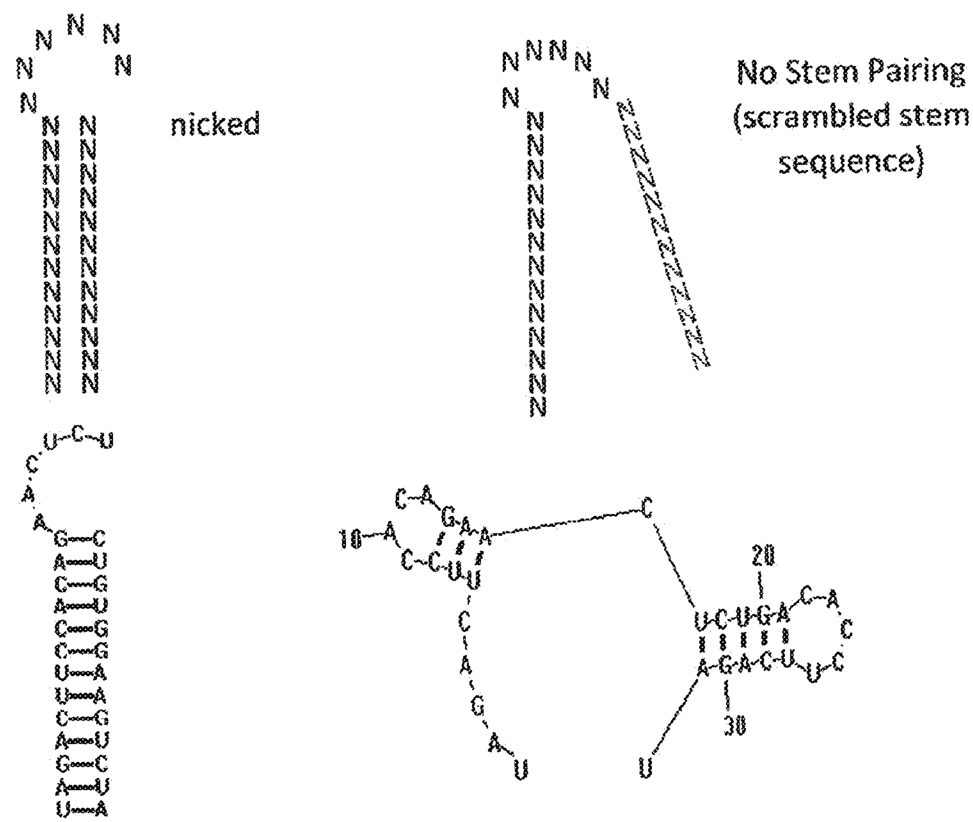

Linoleic acid and cardiolipin enriched micelles
Preferential delivery to heart
HOOC
9Z,12Z-Octadecadienoic Acid (9c12c-C18:2, Linoleic Acid)
Intralipid type composition
Preferential delivery to liver

Figure 12

Figure 13

Structural Elucidation-MAP4K4



12083

12089

Figure 14

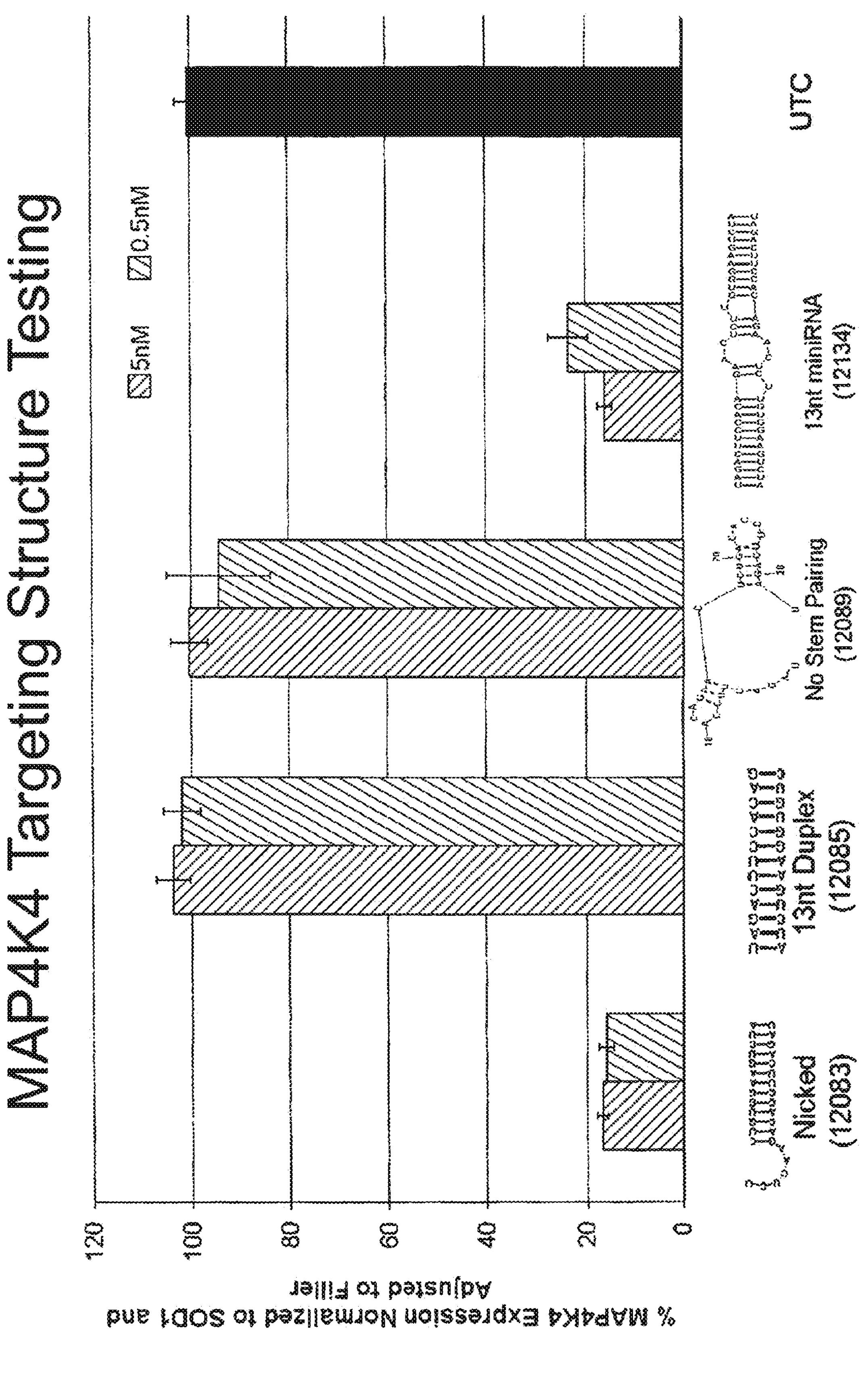

MAP4K4 Targeting Structure Testing
% MAP4K4 Expression Normalized to SOD1 and Adjusted to Filler
120
100
80
60
40
20
0
5nM
0.5nM
Nicked (12083)
13nt Duplex (12085)
No Stem Pairing (12089)
13nt miniRNA (12134)
UTC

Figure 15

MAP4K4 Minimum Length RNAi Trigger

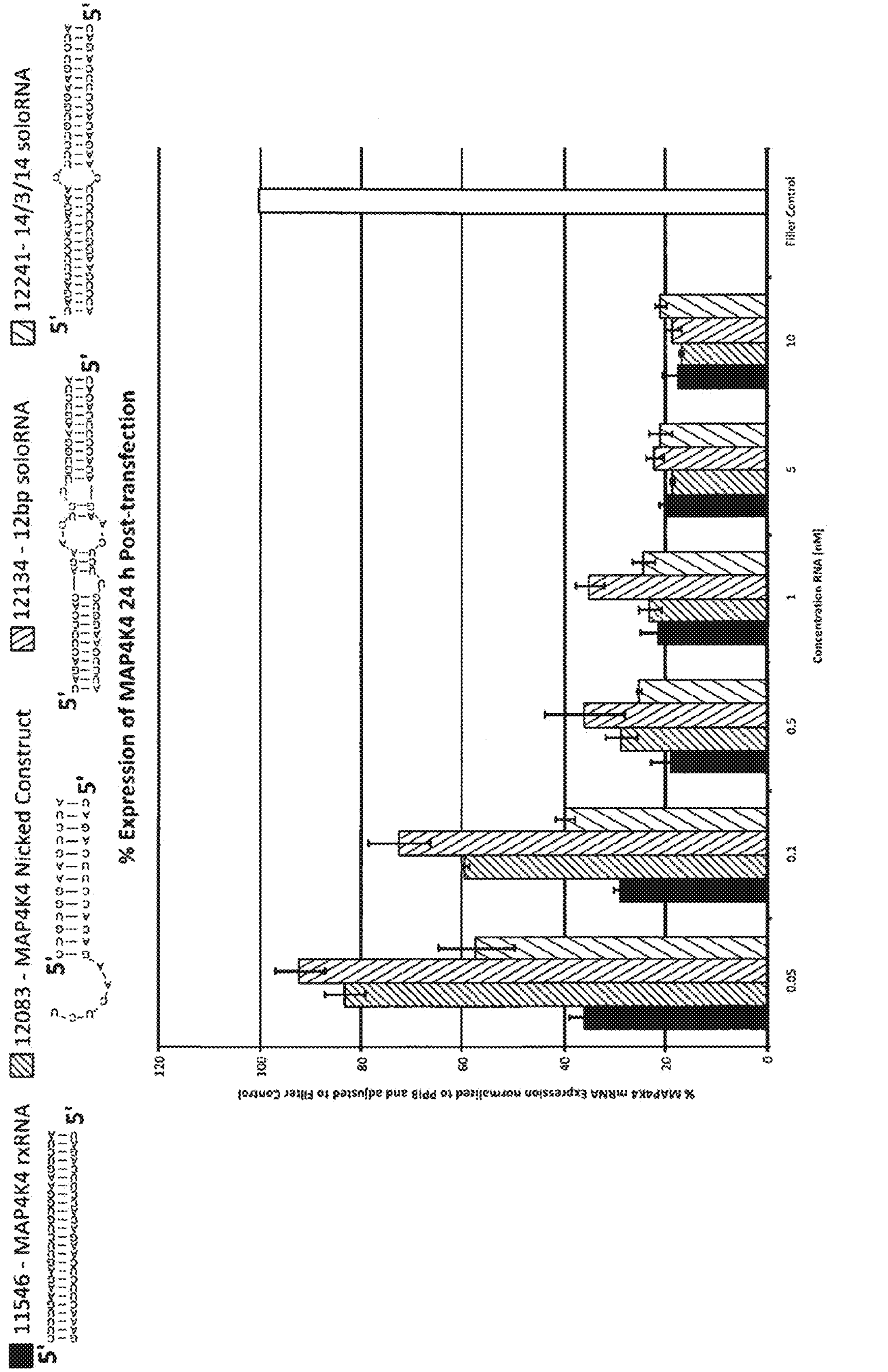
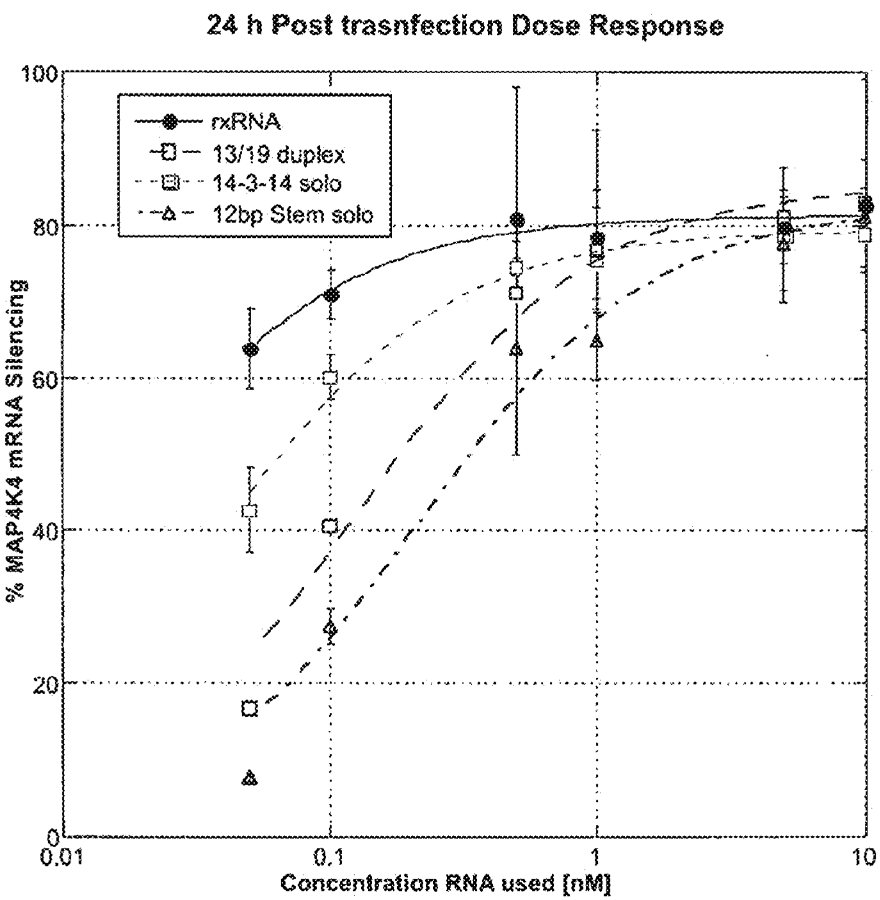
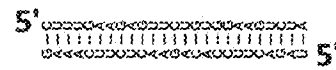


Figure 16

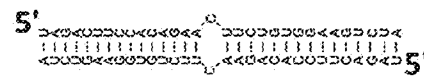
MAP4K4 EC50 Analysis



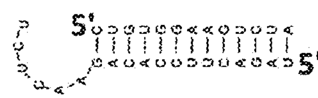
rxRNA		
	Value	Error
m1	81.465	0.83156
EC50	0.013787	0.0016017
Chisq	9.7585	NA
R	0.98118	NA



14-3-14 soloRNA		
	Value	Error
m1	79.605	1.0706
EC50	0.03838	0.0034002
Chisq	14.538	NA
R	0.99297	NA



13/19 duplex (nicked construct)		
	Value	Error
m1	85.386	2.9199
EC50	0.12873	0.022477
Chisq	79.941	NA
R	0.98888	NA



12-bp soloRNA		
	Value	Error
m1	82.734	3.8876
EC50	0.217	0.048933
Chisq	113.39	NA
R	0.98697	NA

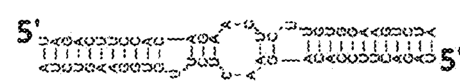


Figure 17

Structural Elucidation-SOD1

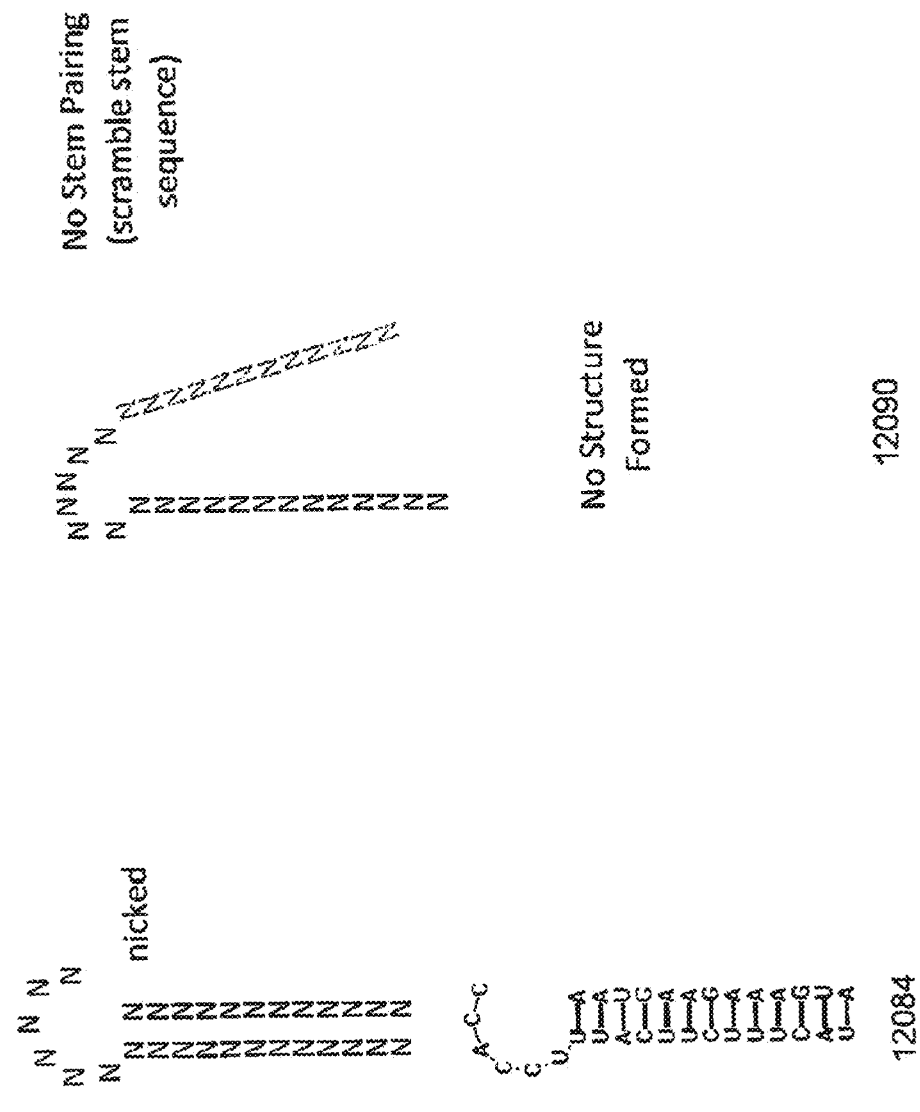


Figure 18

SOD1 Targeting Structure Testing

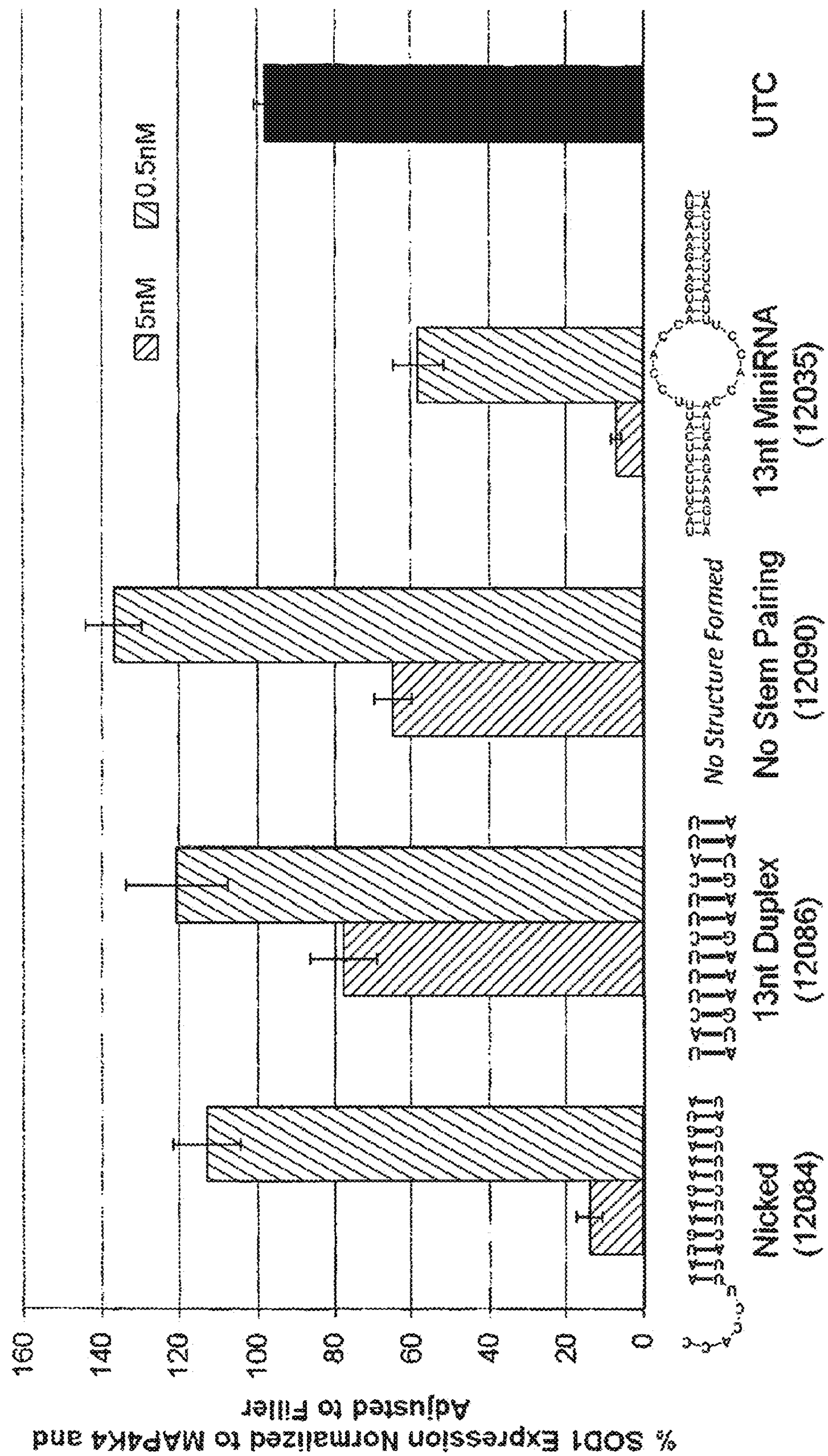


Figure 19

SOD1 Minimum Length RNAi Trigger

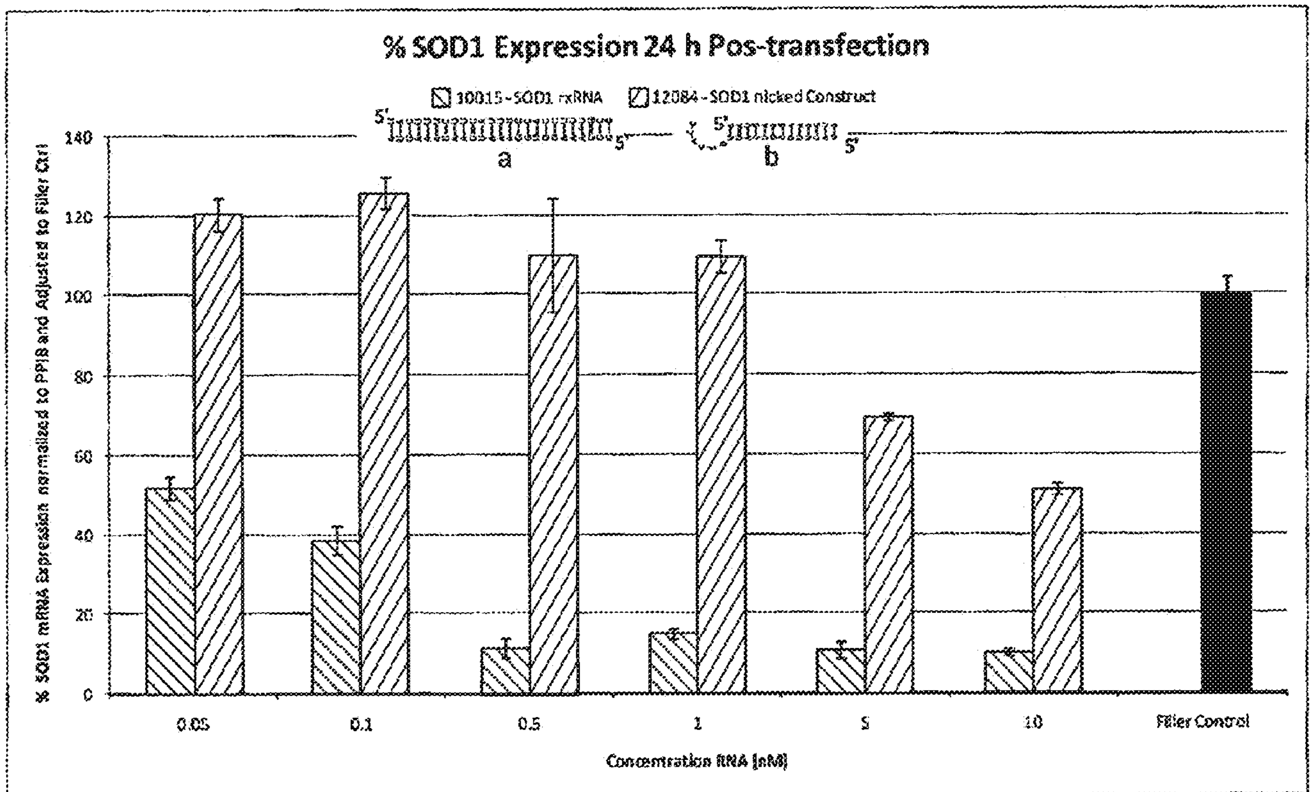


Figure 20

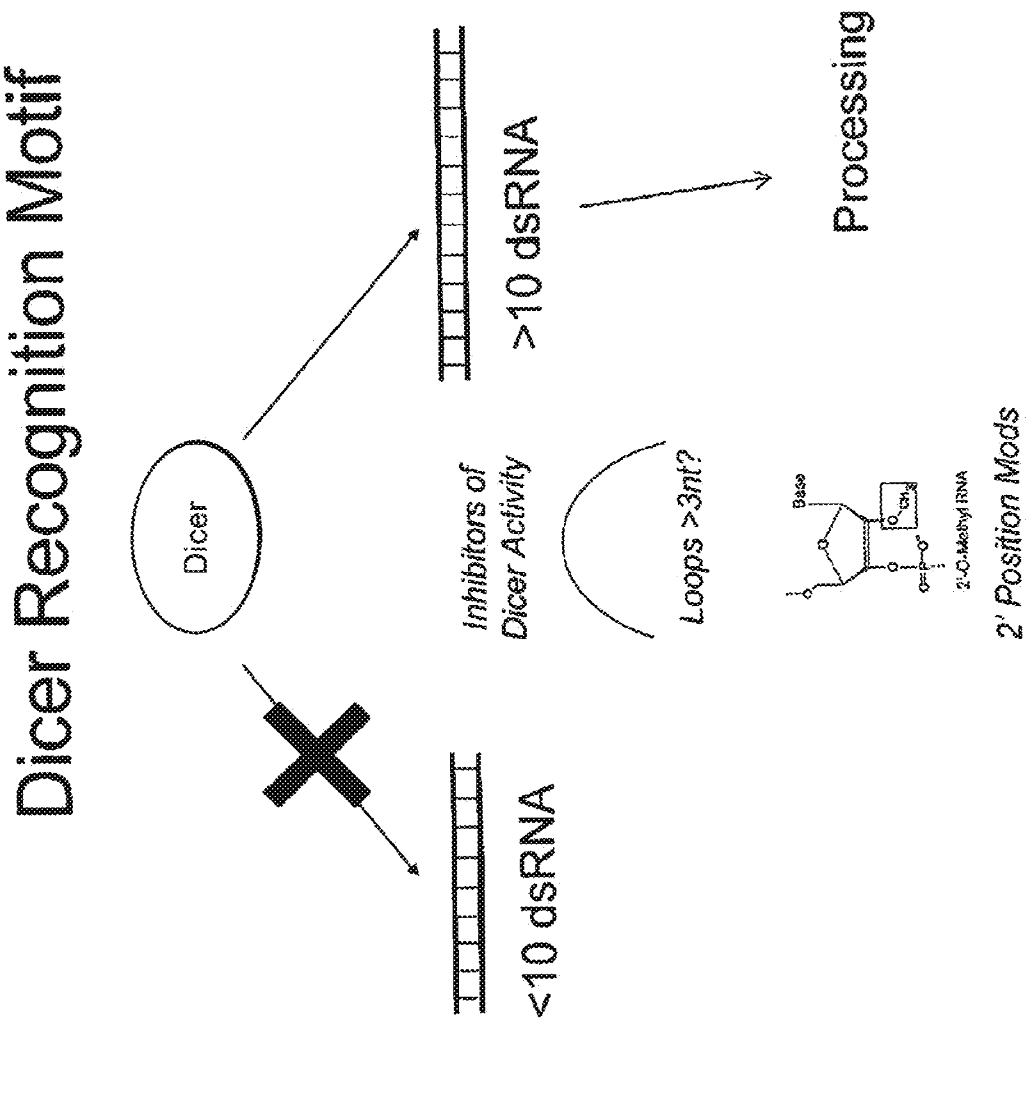

Dicer Recognition Motif
Dicer
>10 dsRNA
Processing
<10 dsRNA
Inhibitors of Dicer Activity
Loops >3nt?
Base
2'-O-Methyl RNA
2' Position Mods

Figure 21

Hypothetical RNAi Model

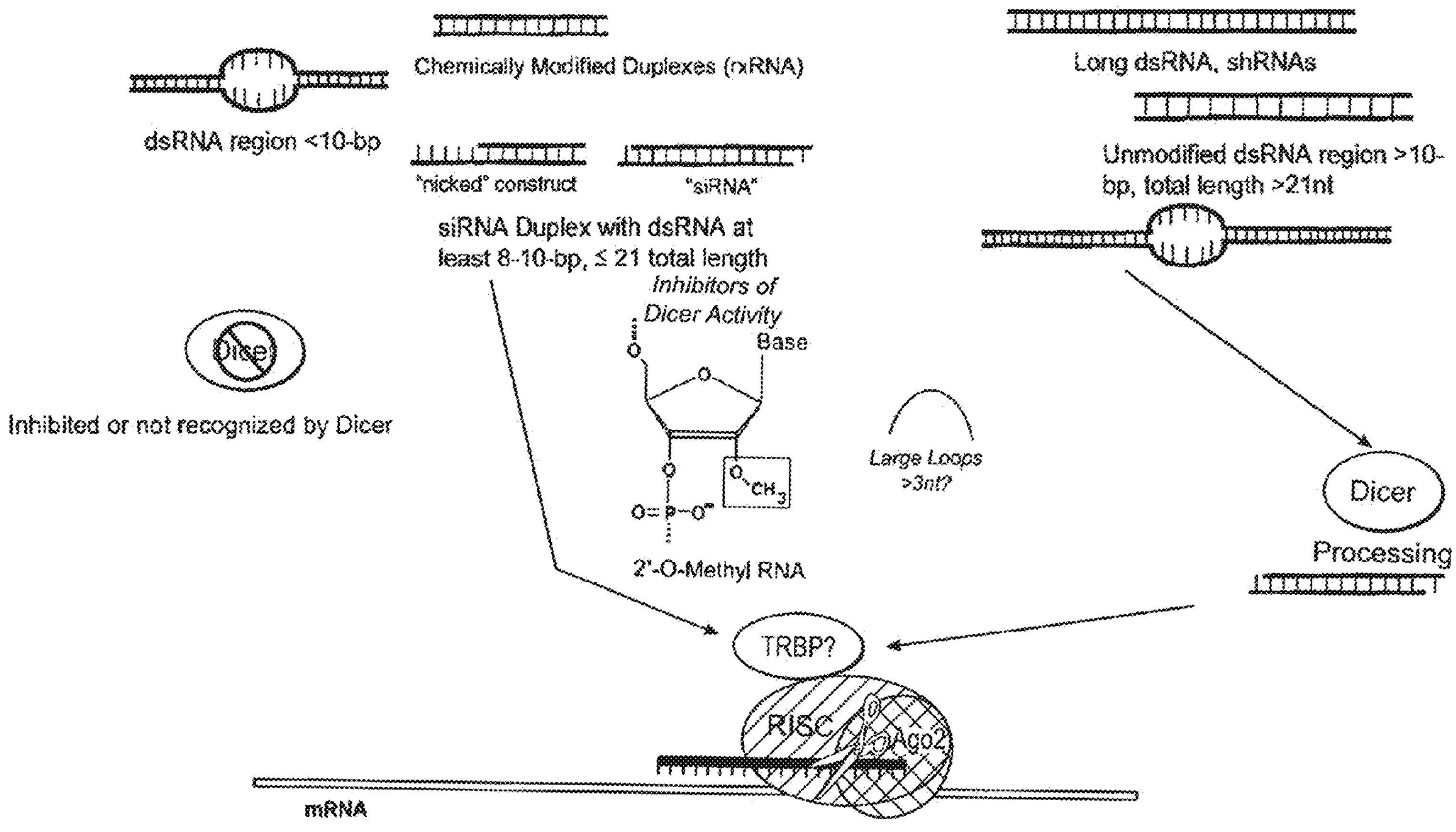


Figure 22

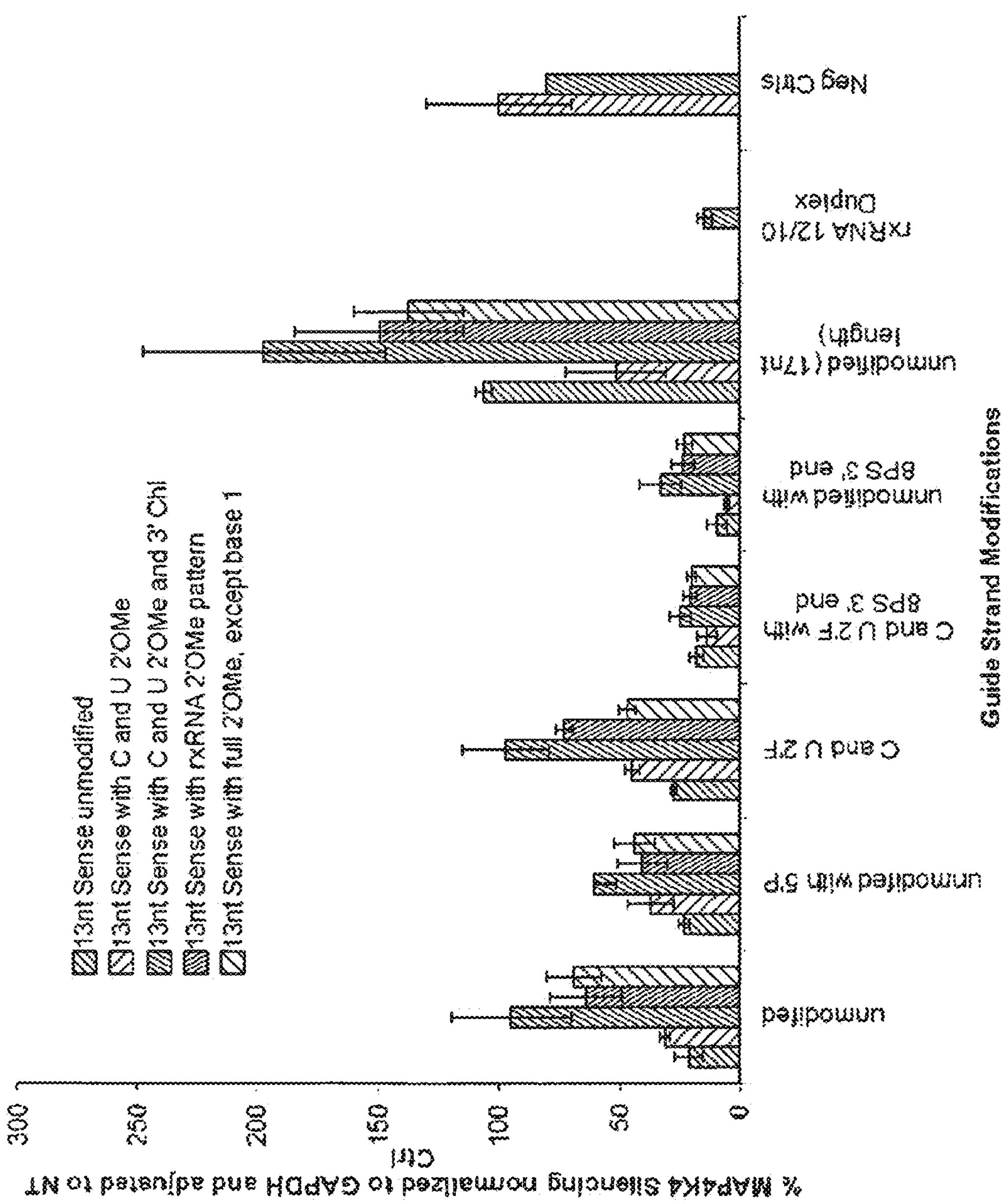

13nt Sense unmodified
13nt Sense with C and U 2'OMe
13nt Sense with C and U 2'OMe and 3' Chl
13nt Sense with rxRNA 2'OMe pattern
13nt Sense with full 2'OMe, except base 1
% MAP4K4 Silencing normalized to GAPDH and adjusted to NT
Ctrl
300
250
200
150
100
50
0
unmodified
unmodified with 5'P
C and U 2'F
C and U 2'F with 8PS 3' end
unmodified with 8PS 3' end
unmodified (17nt length)
rxRNA 12/10 Duplex
Neg Ctrls
Guide Strand Modifications

Figure 23

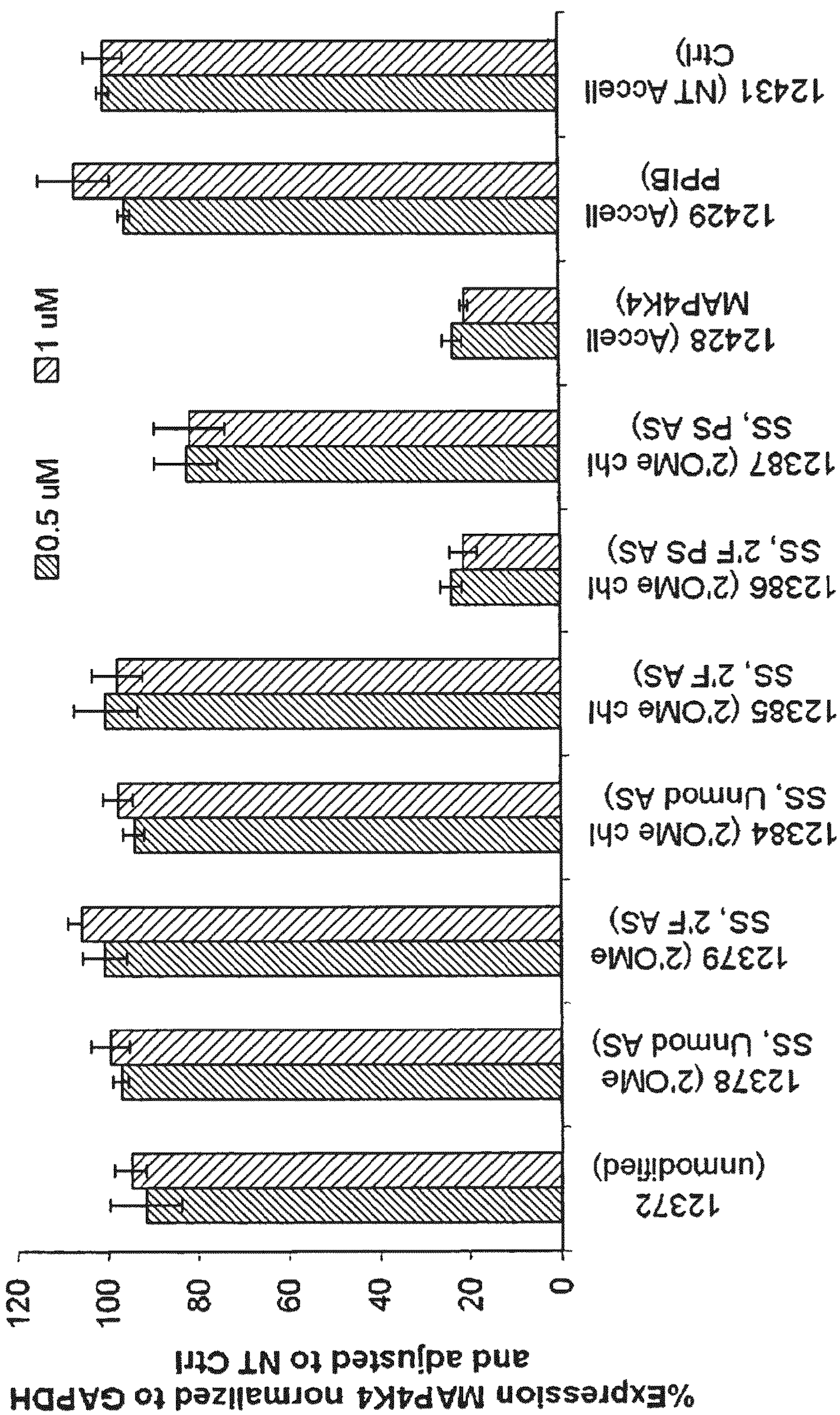

%Expression MAP4K4 normalized to GAPDH and adjusted to NT Ctrl
0
20
40
60
80
100
120
0.5 uM
1 uM
12372 (unmodified)
12378 (2'OMe SS, Unmod AS)
12379 (2'OMe SS, 2'F AS)
12384 (2'OMe chl SS, Unmod AS)
12385 (2'OMe chl SS, 2'F AS)
12386 (2'OMe chl SS, 2'F PS AS)
12387 (2'OMe chl SS, PS AS)
12428 (Accell MAP4K4)
12429 (Accell PPIB)
12431 (NT Accell Ctrl)

Figure 24

Self-Delivering nano-rxRNA

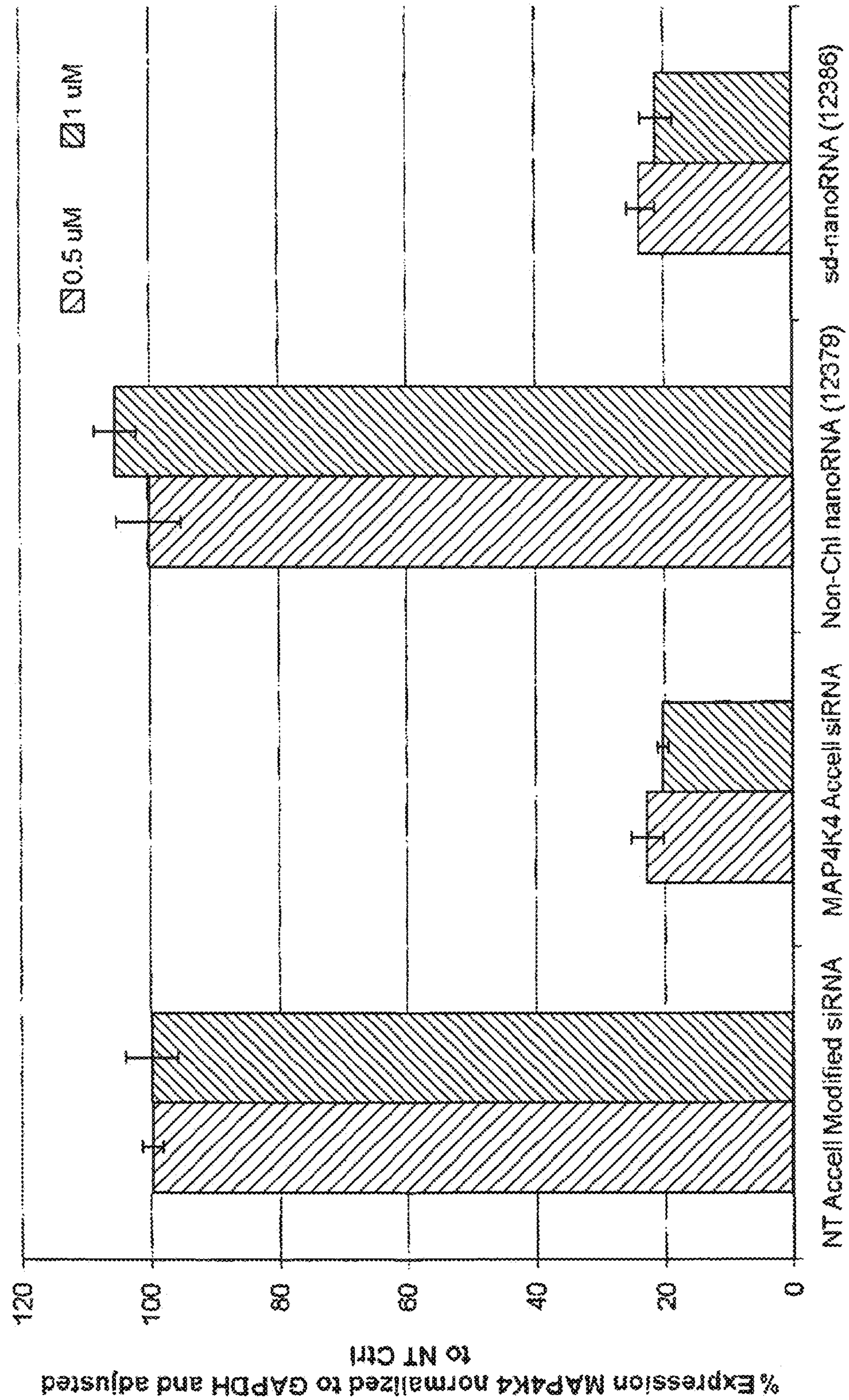
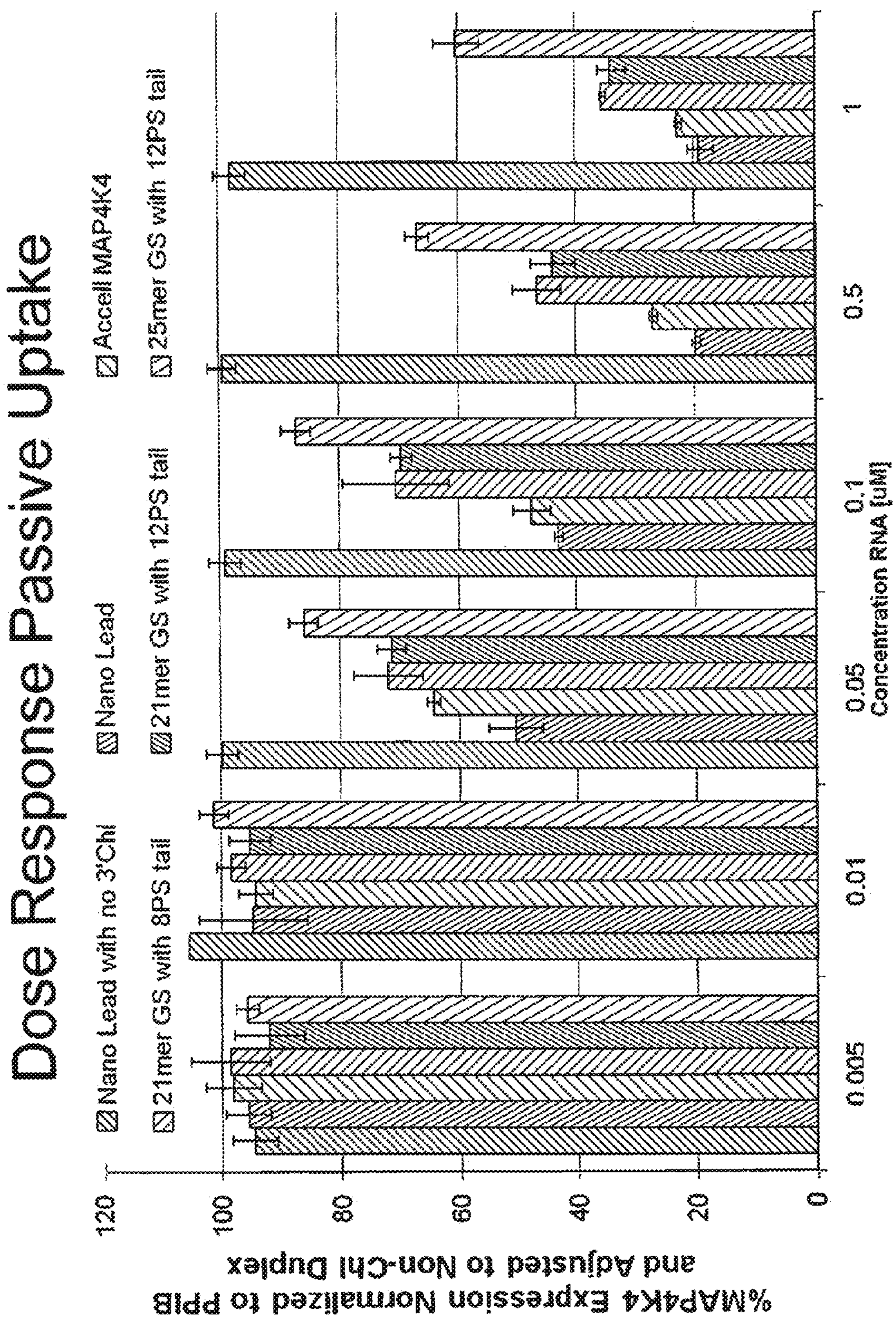
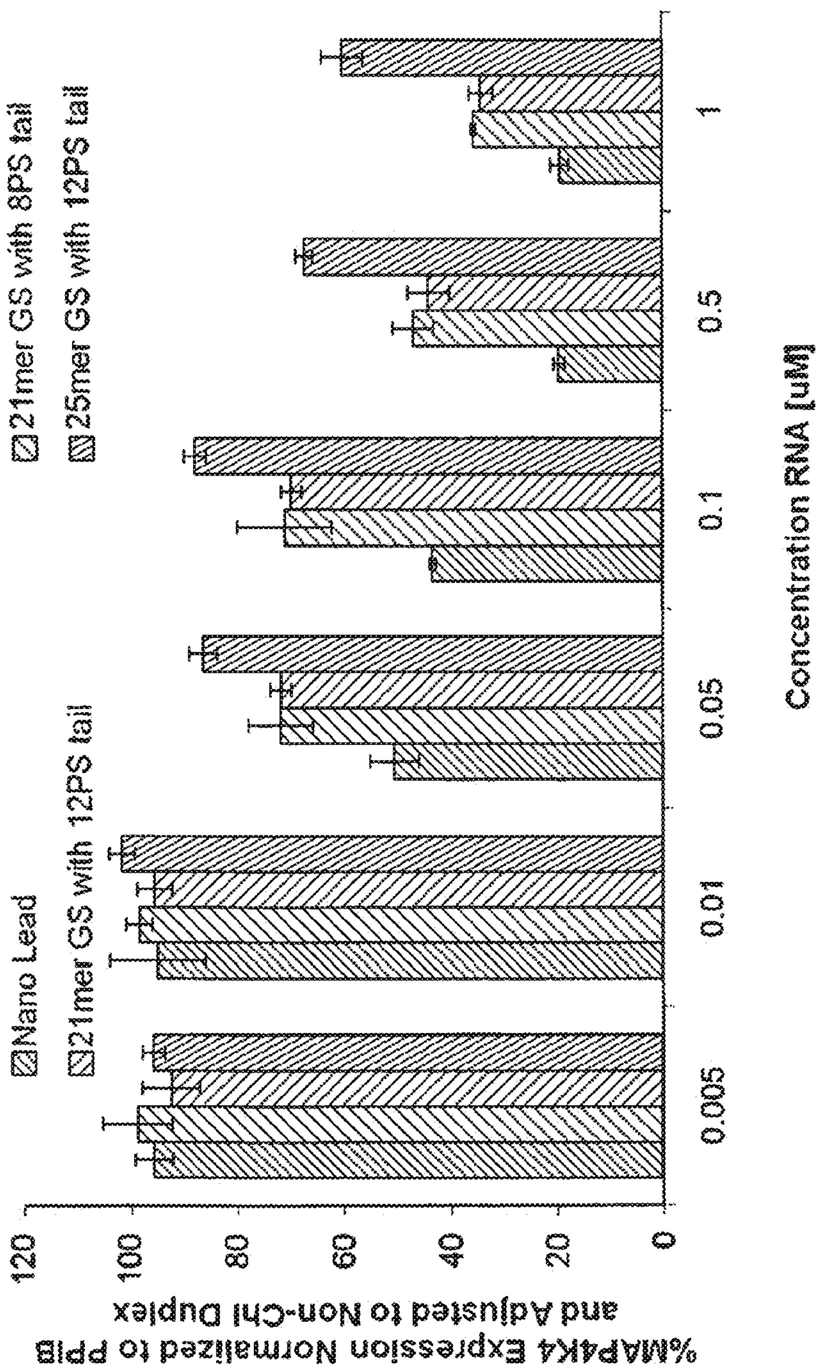


Figure 25



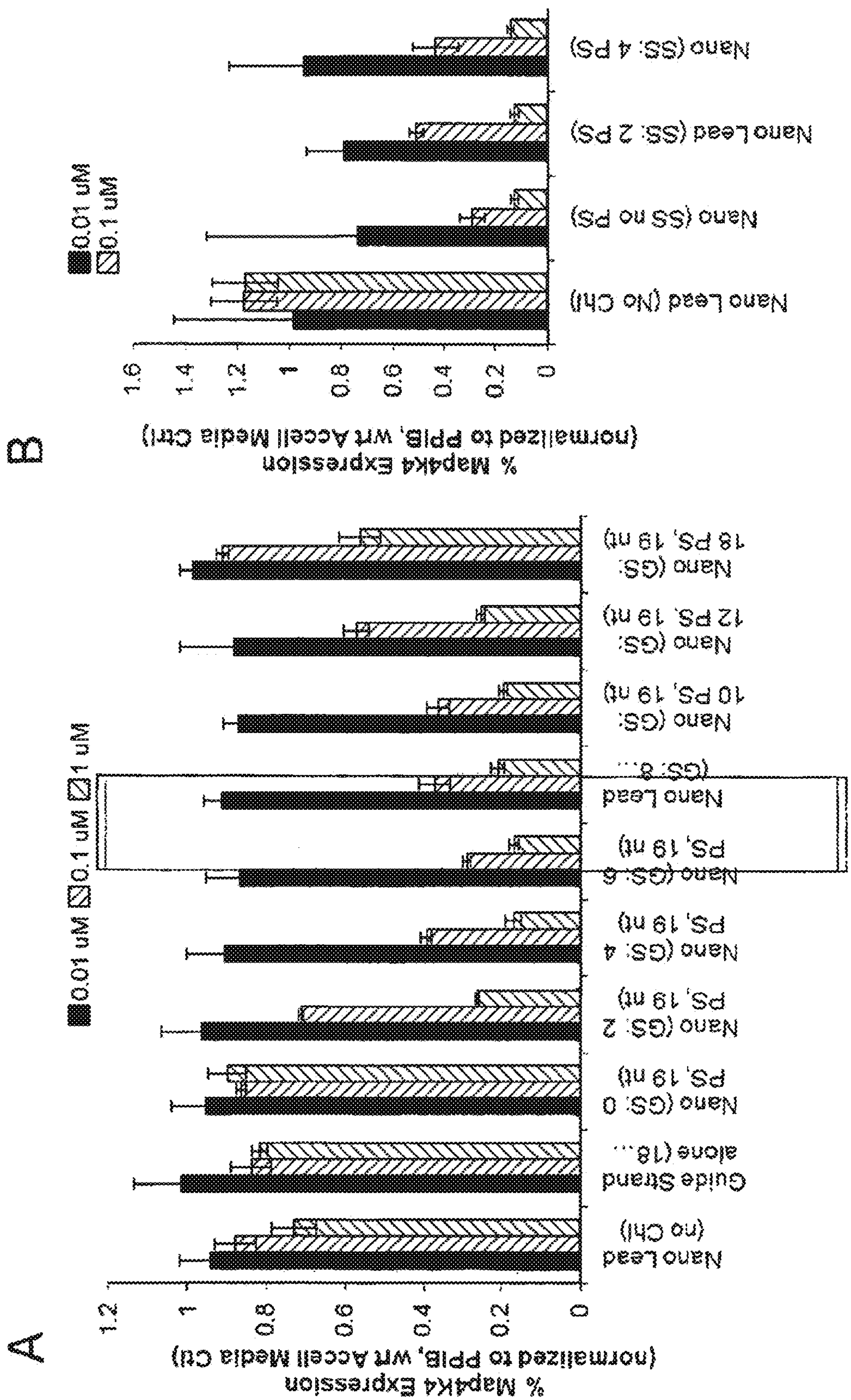
Dose Response Passive Uptake
Nano Lead with no 3'Chl
Nano Lead
Accell MAP4K4
21mer GS with 8PS tail
21mer GS with 12PS tail
25mer GS with 12PS tail
%MAP4K4 Expression Normalized to PPIB and Adjusted to Non-Chl Duplex
120
100
80
60
40
20
0
0.005
0.01
0.05
0.1
0.5
1
Concentration RNA [uM]

Figure 26



Nano Lead
21mer GS with 12PS tail
21mer GS with 8PS tail
25mer GS with 12PS tail
%MAP4K4 Expression Normalized to PPIB and Adjusted to Non-Chl Duplex
120
100
80
60
40
20
0
0.005
0.01
0.05
0.1
0.5
1
Concentration RNA [uM]

Figure 27



A
% Mapk4 Expression
(normalized to PPIB, wrt Accell Media Ctl)
0.01 uM
0.1 uM
1 uM
Nano Lead (no Chl)
Guide Strand alone (18...
Nano (GS: 0 PS, 19 nt)
Nano (GS: 2 PS, 19 nt)
Nano (GS: 4 PS, 19 nt)
Nano (GS: 6 PS, 19 nt)
Nano Lead (GS: 8...
Nano (GS: 10 PS, 19 nt)
Nano (GS: 12 PS, 19 nt)
Nano (GS: 18 PS, 19 nt)
B
% Mapk4 Expression
(normalized to PPIB, wrt Accell Media Ctrl)
0.01 uM
0.1 uM
Nano Lead (No Chl)
Nano (SS no PS)
Nano Lead (SS: 2 PS)
Nano (SS: 4 PS)

Figure 28

sd-nanoRNA silencing in Primary Mouse Hepatocytes

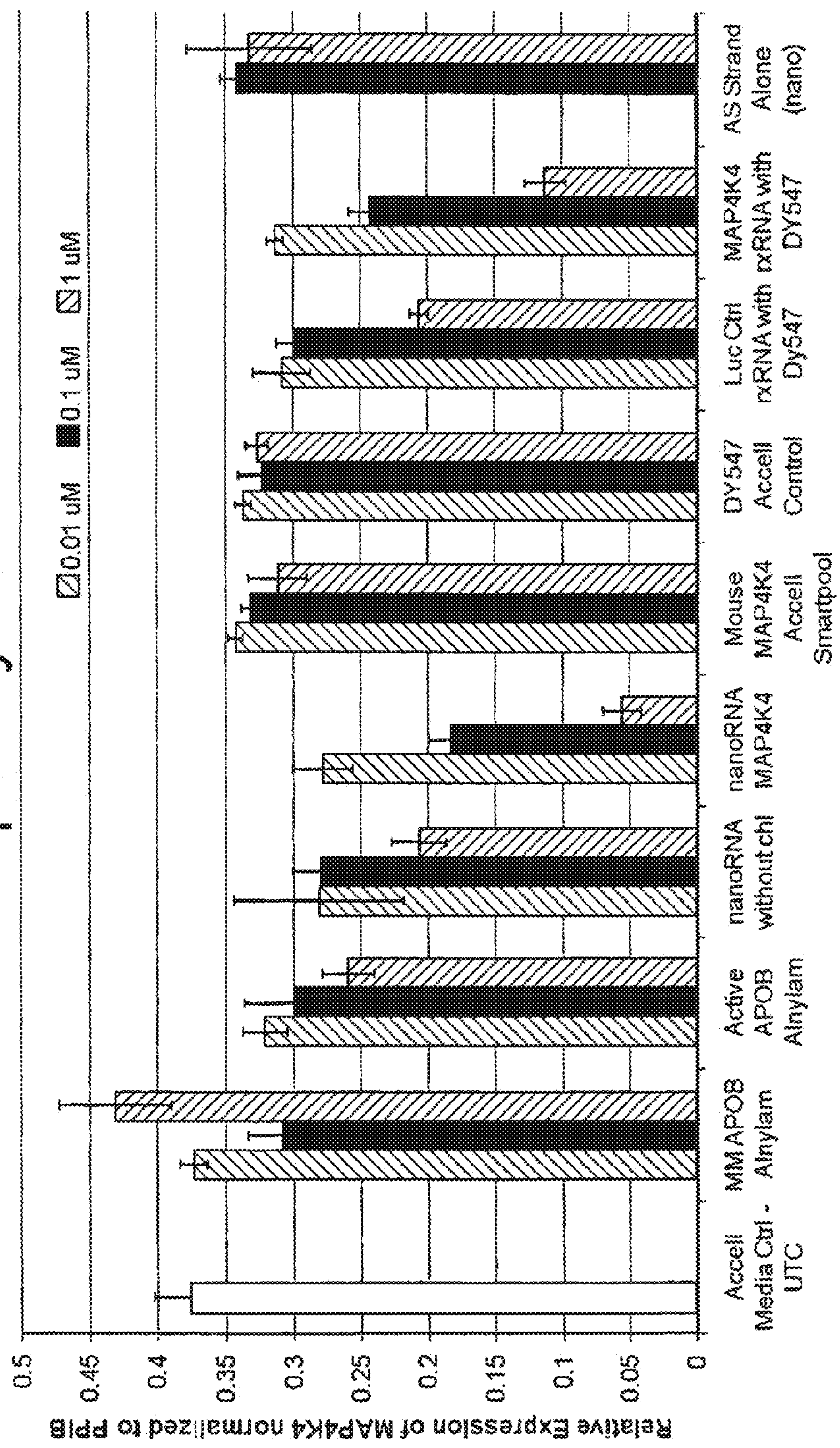


Figure 29

Passive Uptake with Alnylam siRNA in Primary Mouse Hepatocytes

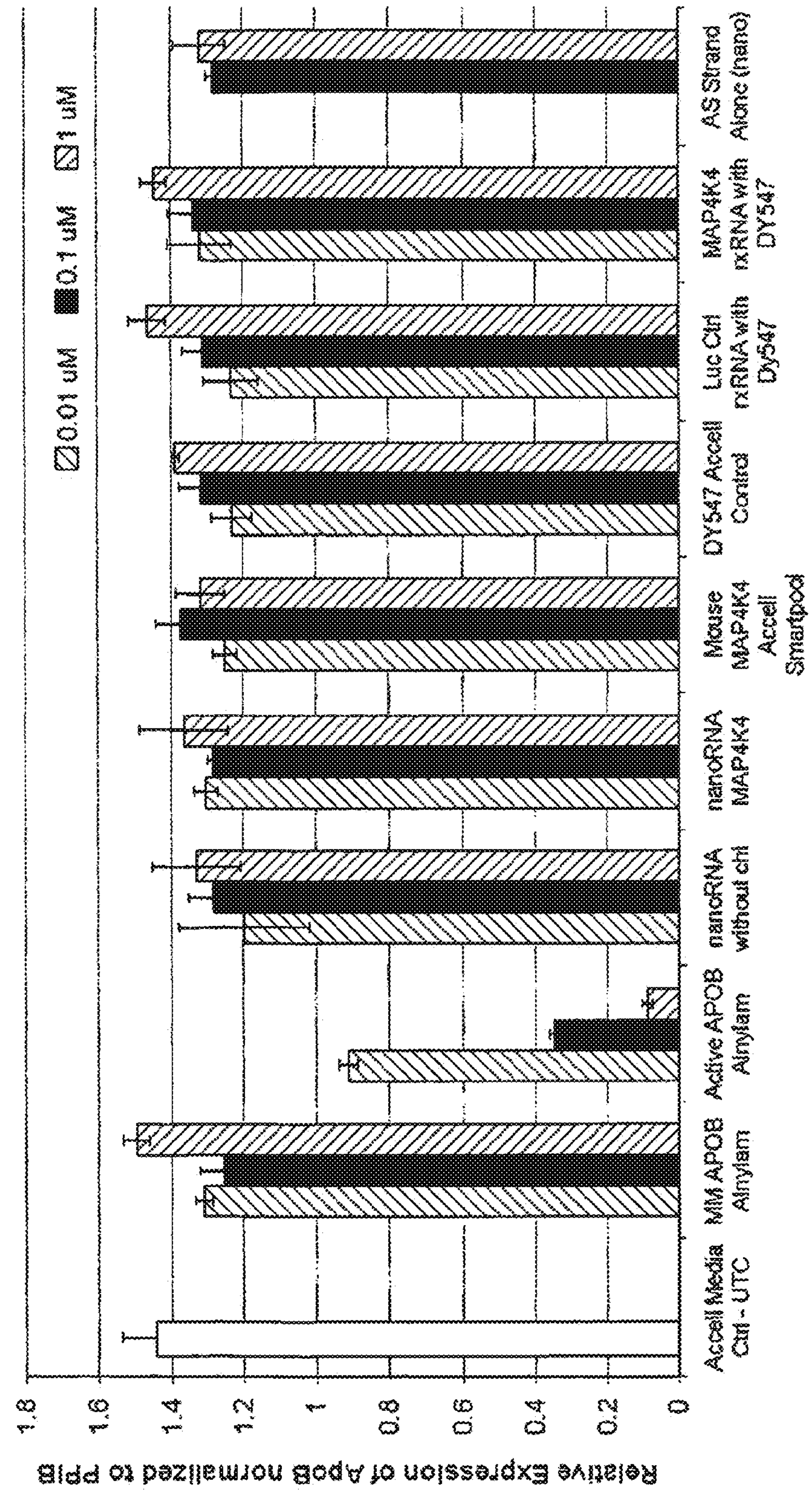


Figure 30

Sd-nanoRNA can silence genes in Primary Human Hepatocytes

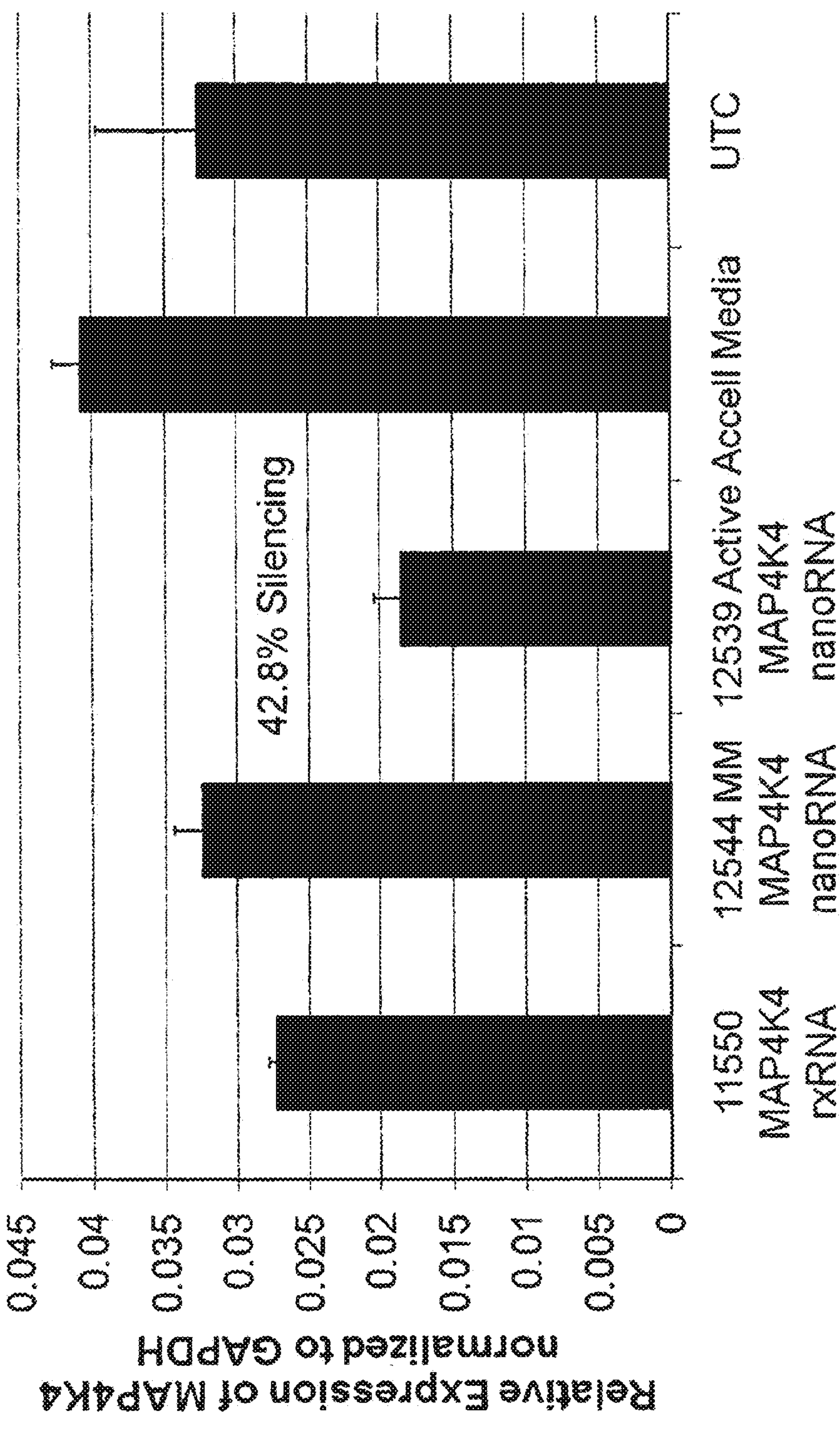


Figure 31

chol-siRNA silencing in Primary Human Hepatocytes

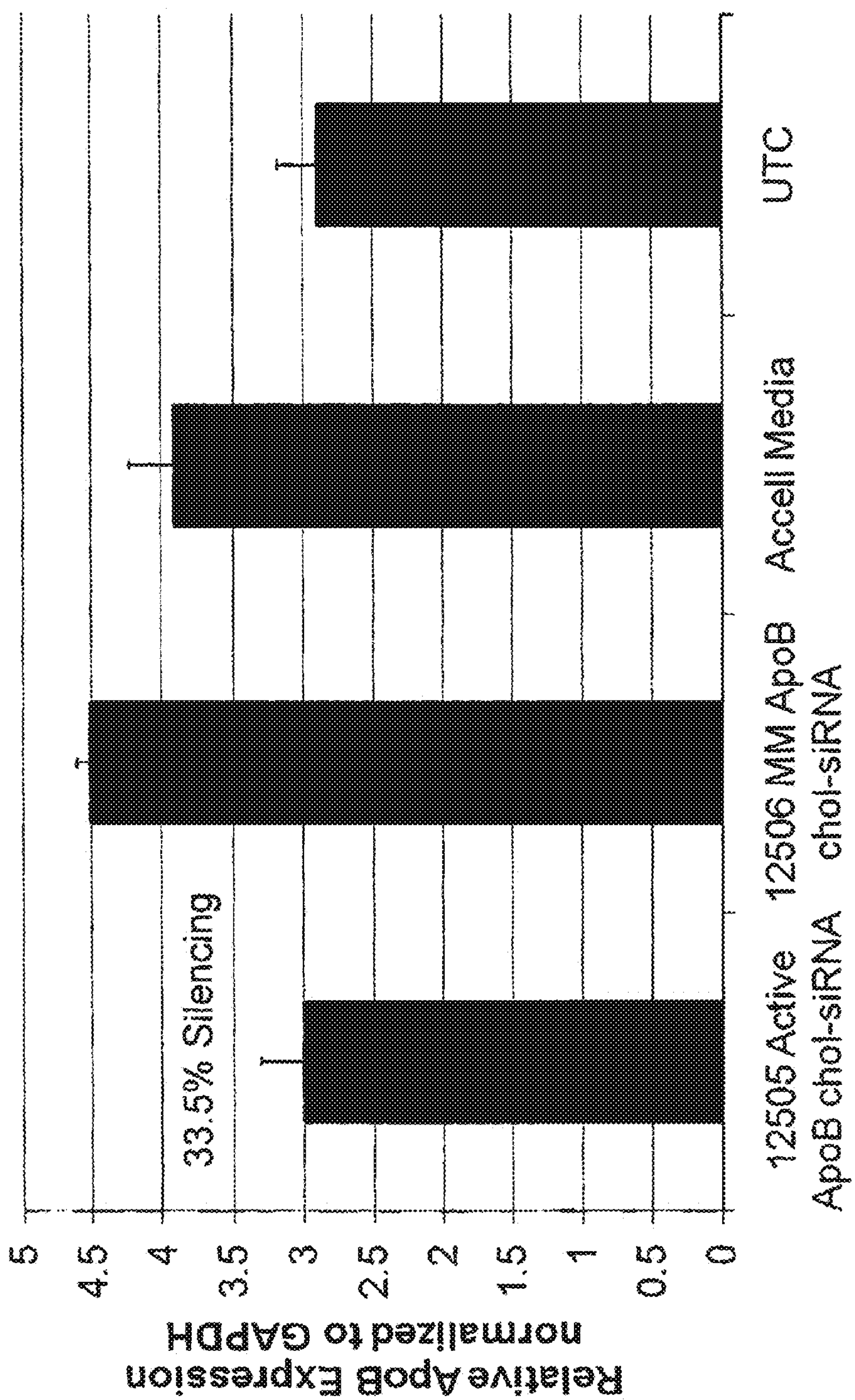


Figure 32

sd-rxRNA^{nano} Localization

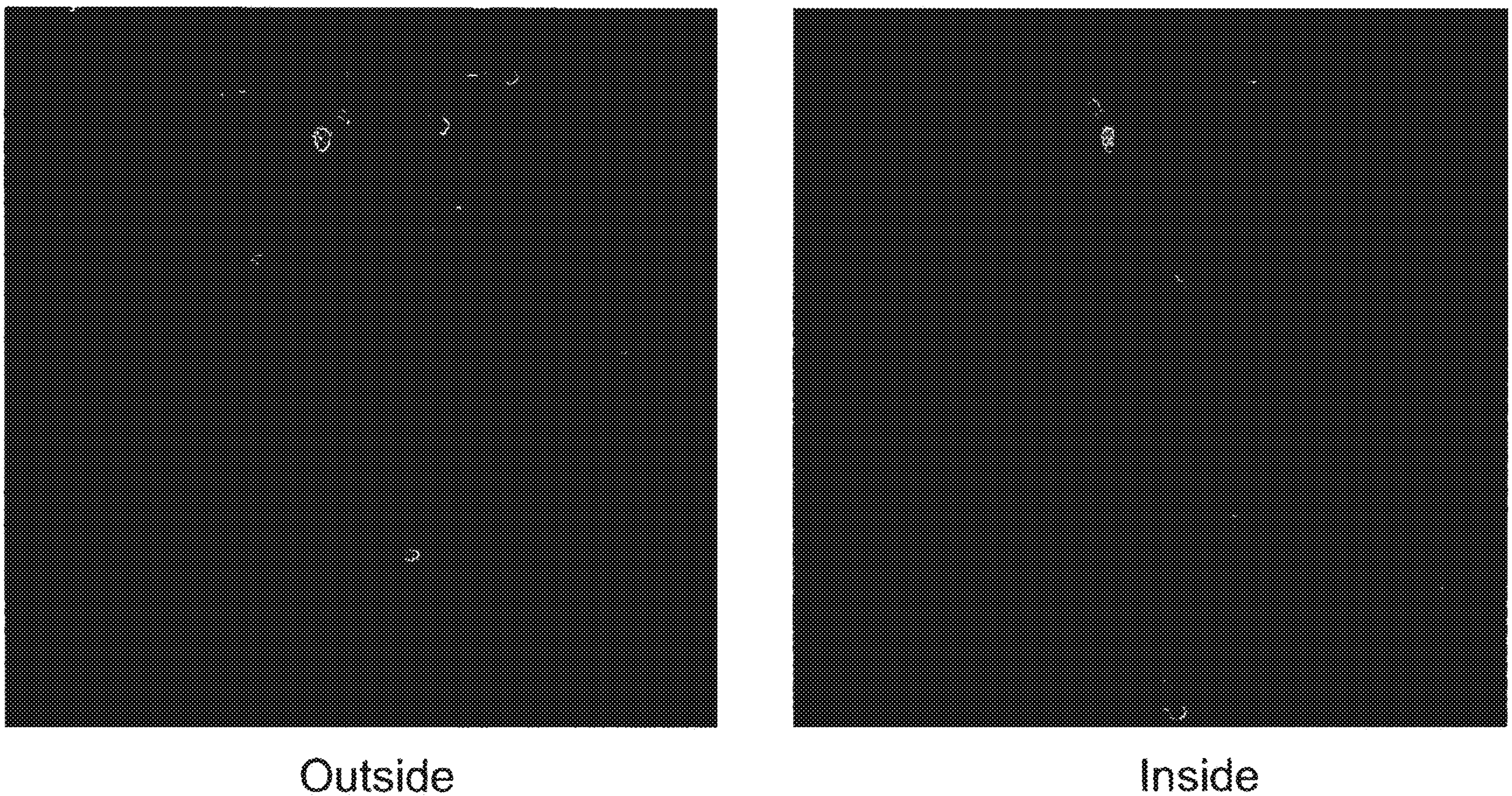
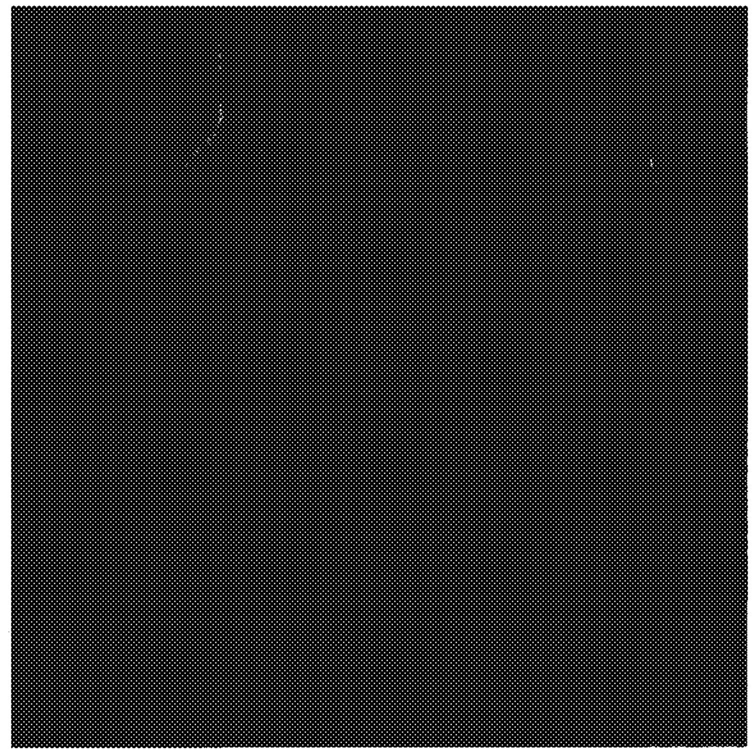


Figure 33

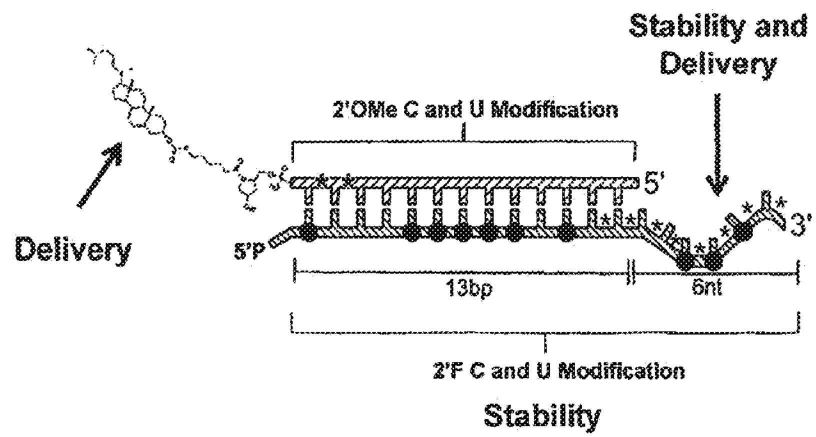
Chol-siRNA (Alnylam) Localization

Outside



Inside

1st Generation sd-rxRNA^{nano}

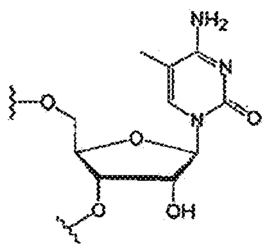


- Why do we need to optimize chemistry?
  - Increased potency
    - Nucleotide Length
    - PS Content
  - Reduced toxicity
    - Replacing 2'F on GS
  - Delivery
    - Linker and Sterol modalities
  - Ease of manufacturing
    - Replacing OH-PS

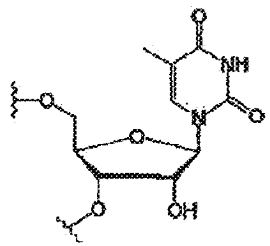
Key
* Phosphorothioate
● 2' F

Figure 34

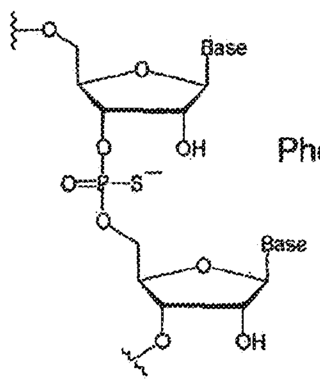
Chemical Modifications Screened for Optimization of sd-rxRNA^{nano} (G1)



5-Methyl Cytidine
(5-Me C)



riboThymidine
(rT)



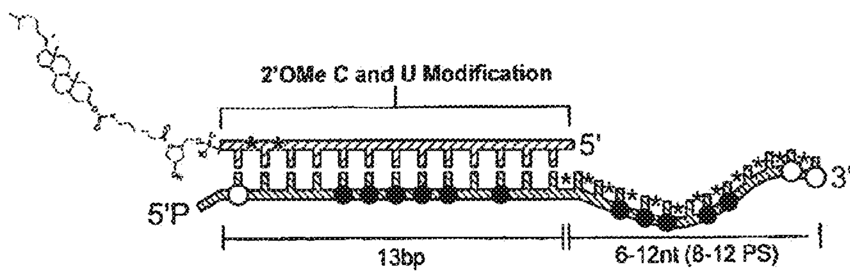
Phosphorothioate
linkage

Above pictures from
www.dharmacon.com

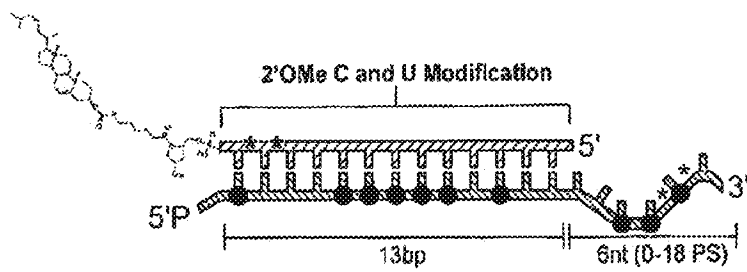
Figure 35

Optimization of GS Length and PS Content

Screen Nucleotide and PS tail length



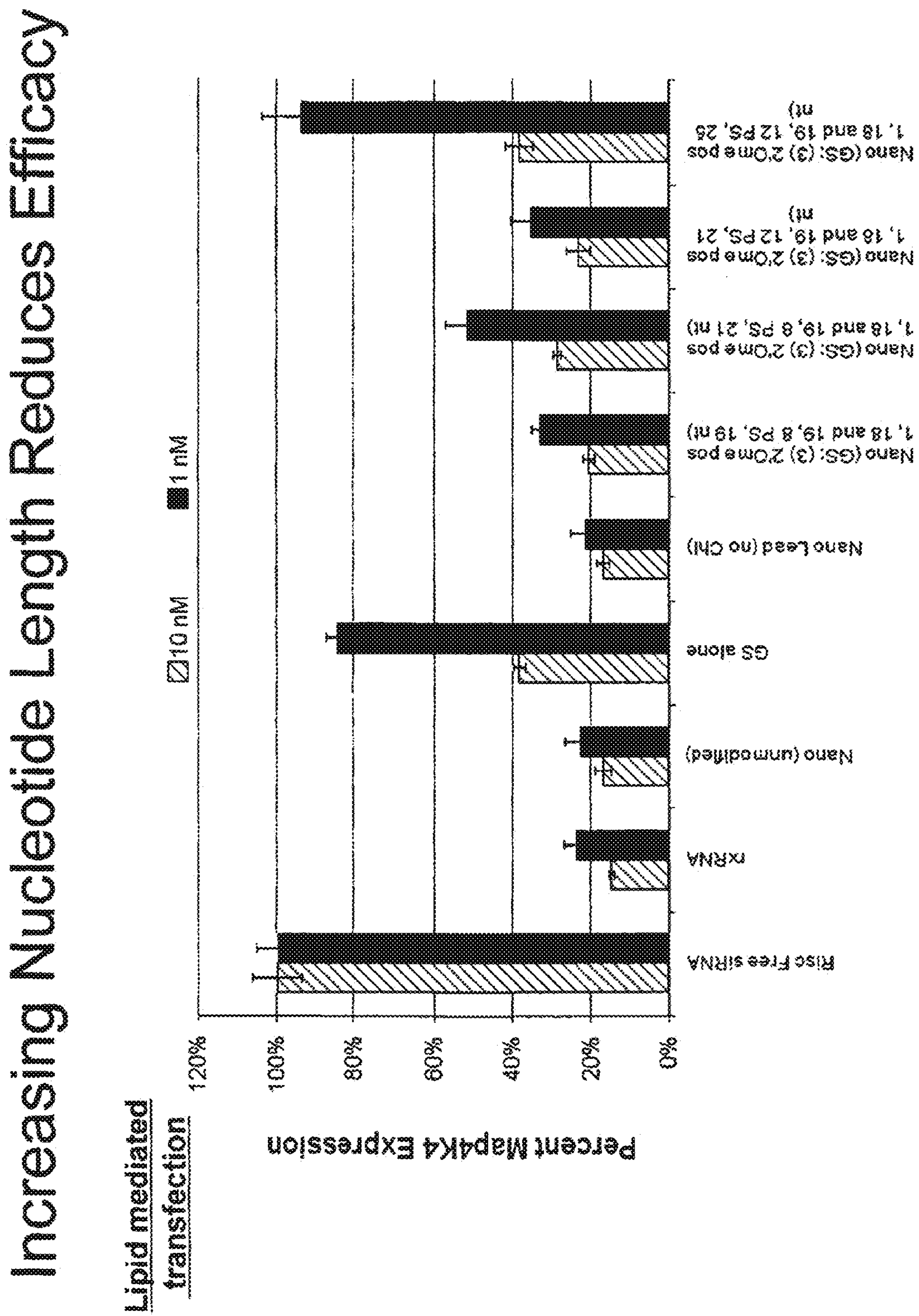
Screen PS content in 19mer



Key

- o 2'OMe
- * Phosphothioate
- ● 2' F

Figure 36



Increasing Nucleotide Length Reduces Efficacy
Lipid mediated transfection
Percent Map4K4 Expression
120%
100%
80%
60%
40%
20%
0%
10 nM
1 nM
Risc Free siRNA
rxRNA
Nano (unmodified)
GS alone
Nano Lead (no Chl)
Nano (GS: (3) 2'Ome pos 1, 18 and 19, 8 PS, 19 nt)
Nano (GS: (3) 2'Ome pos 1, 18 and 19, 8 PS, 21 nt)
Nano (GS: (3) 2'Ome pos 1, 18 and 19, 12 PS, 21 nt)
Nano (GS: (3) 2'Ome pos 1, 18 and 19, 12 PS, 26 nt)

Figure 37

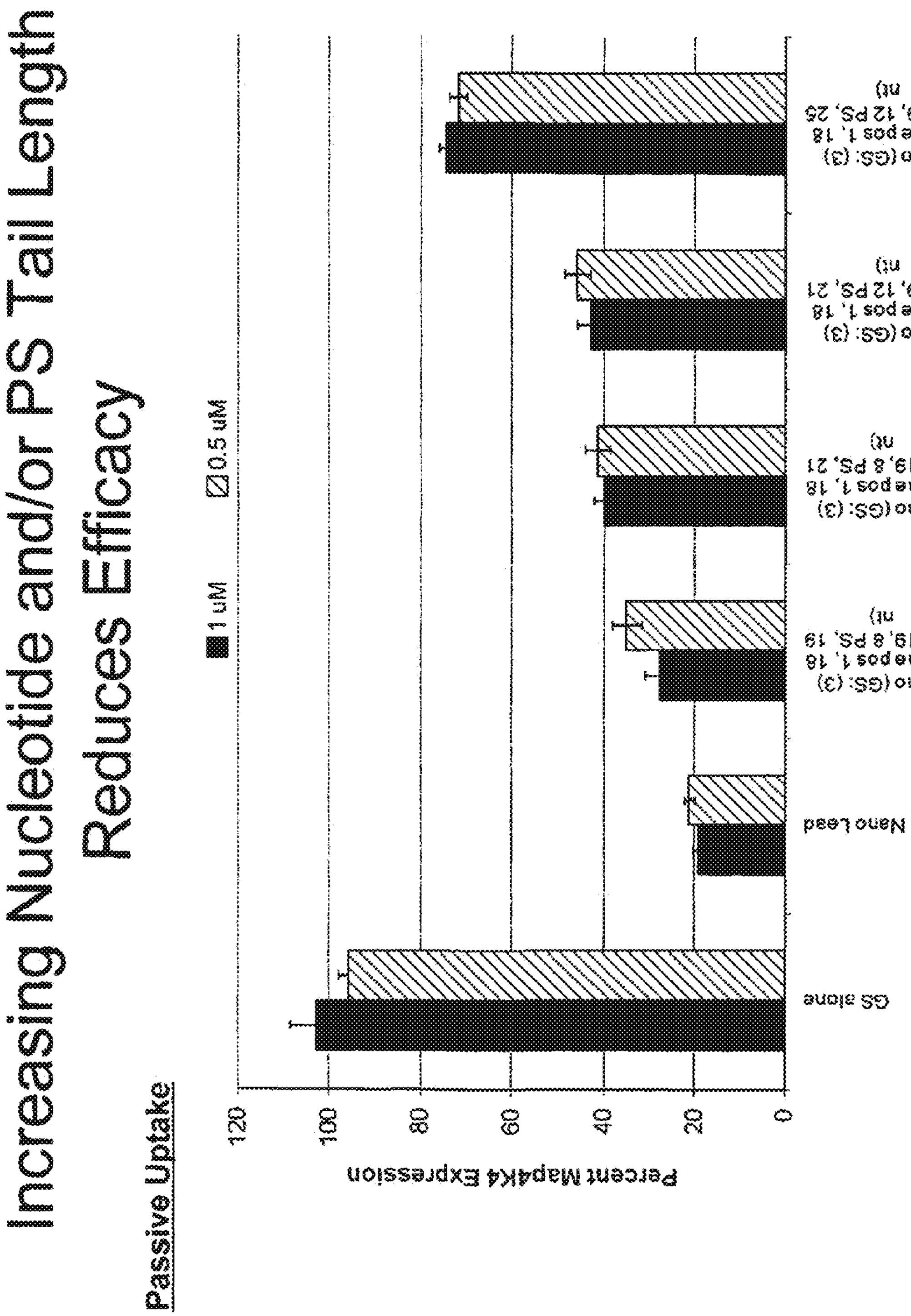

Increasing Nucleotide and/or PS Tail Length Reduces Efficacy
Passive Uptake
1 uM
0.5 uM
Percent Map4K4 Expression
0
20
40
60
80
100
120
GS alone
Nano Lead
Nano (GS: (3) 2'Ome pos 1, 18 and 19, 8 PS, 19 nt)
Nano (GS: (3) 2'Ome pos 1, 18 and 19, 8 PS, 21 nt)
Nano (GS: (3) 2'Ome pos 1, 18 and 19, 12 PS, 21 nt)
Nano (GS: (3) 2'Ome pos 1, 18 and 19, 12 PS, 25 nt)

Figure 38

Figure 39

4 to 10 Phosphorothioates Tolerated in GS (19 mer)

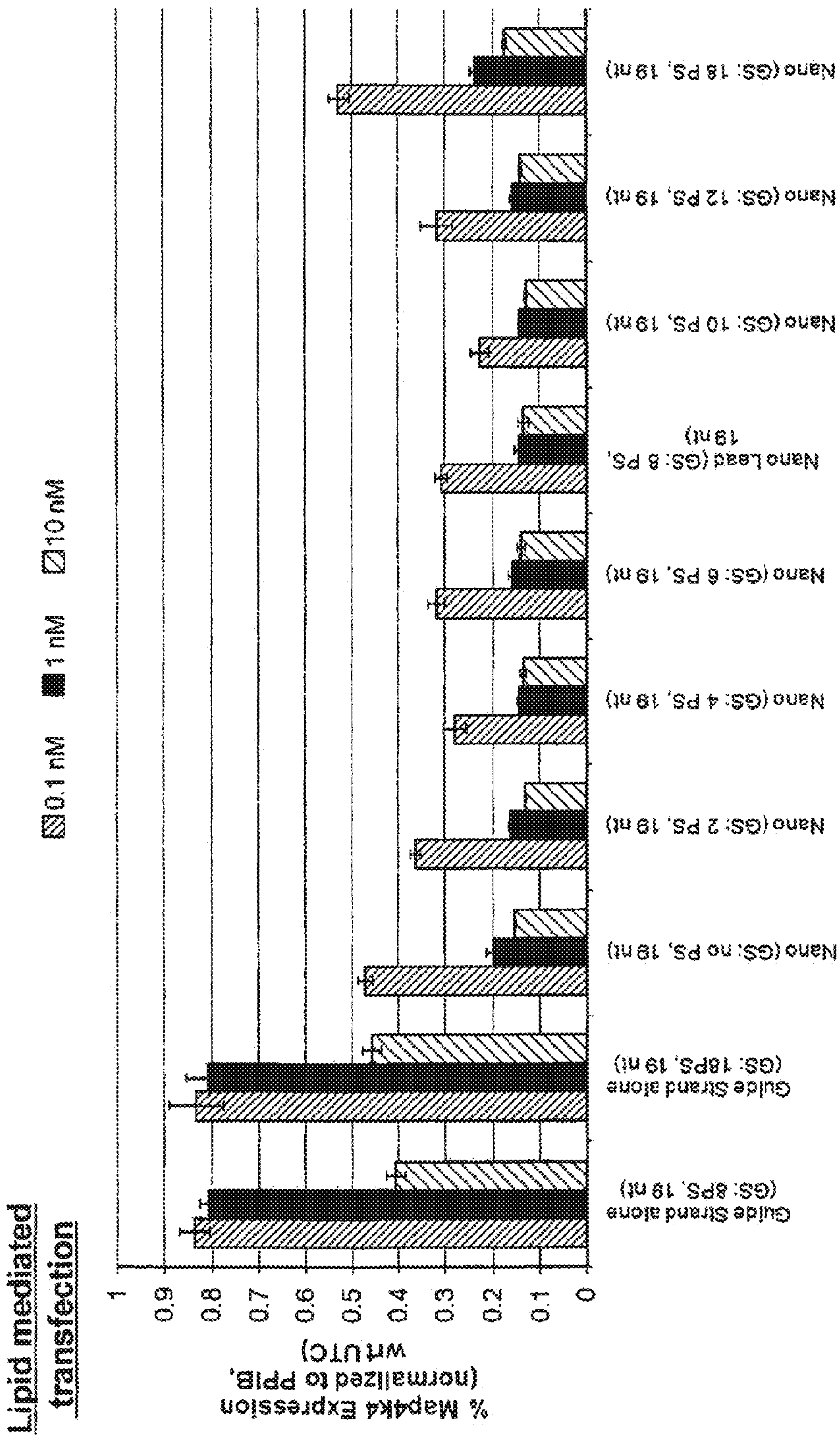
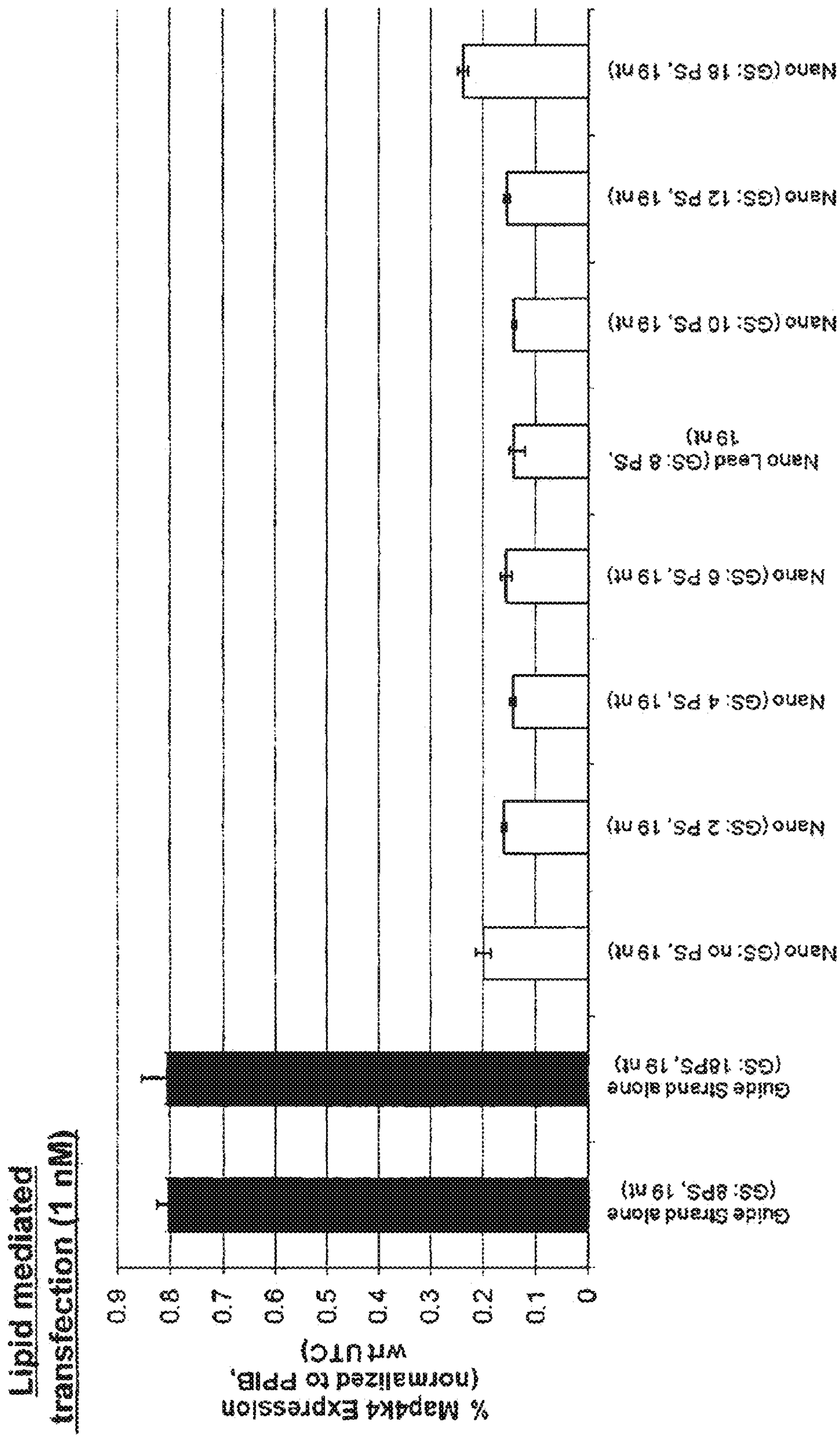


Figure 40

4 to 10 Phosphorothioates Tolerated in GS (19 mer)



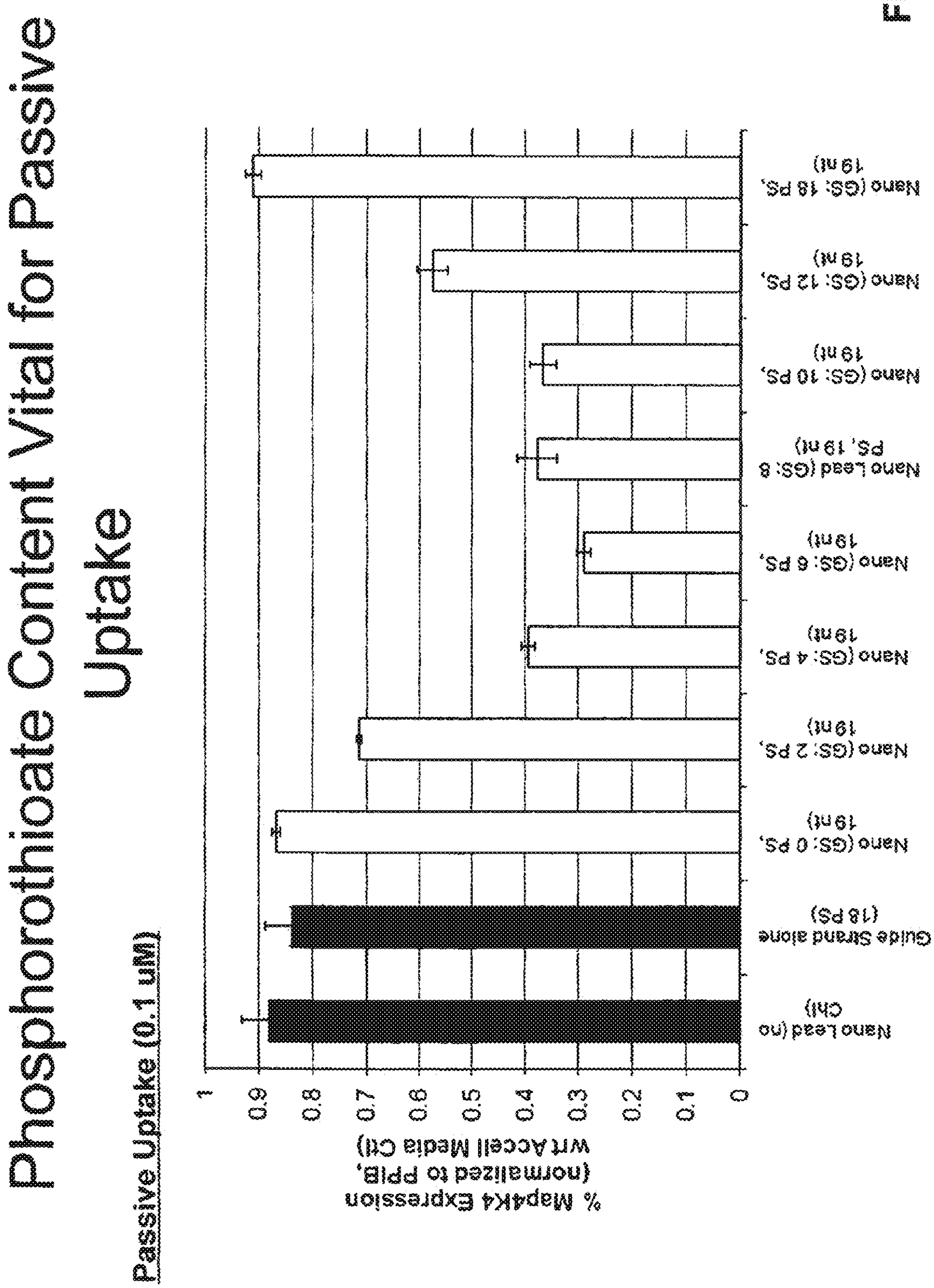
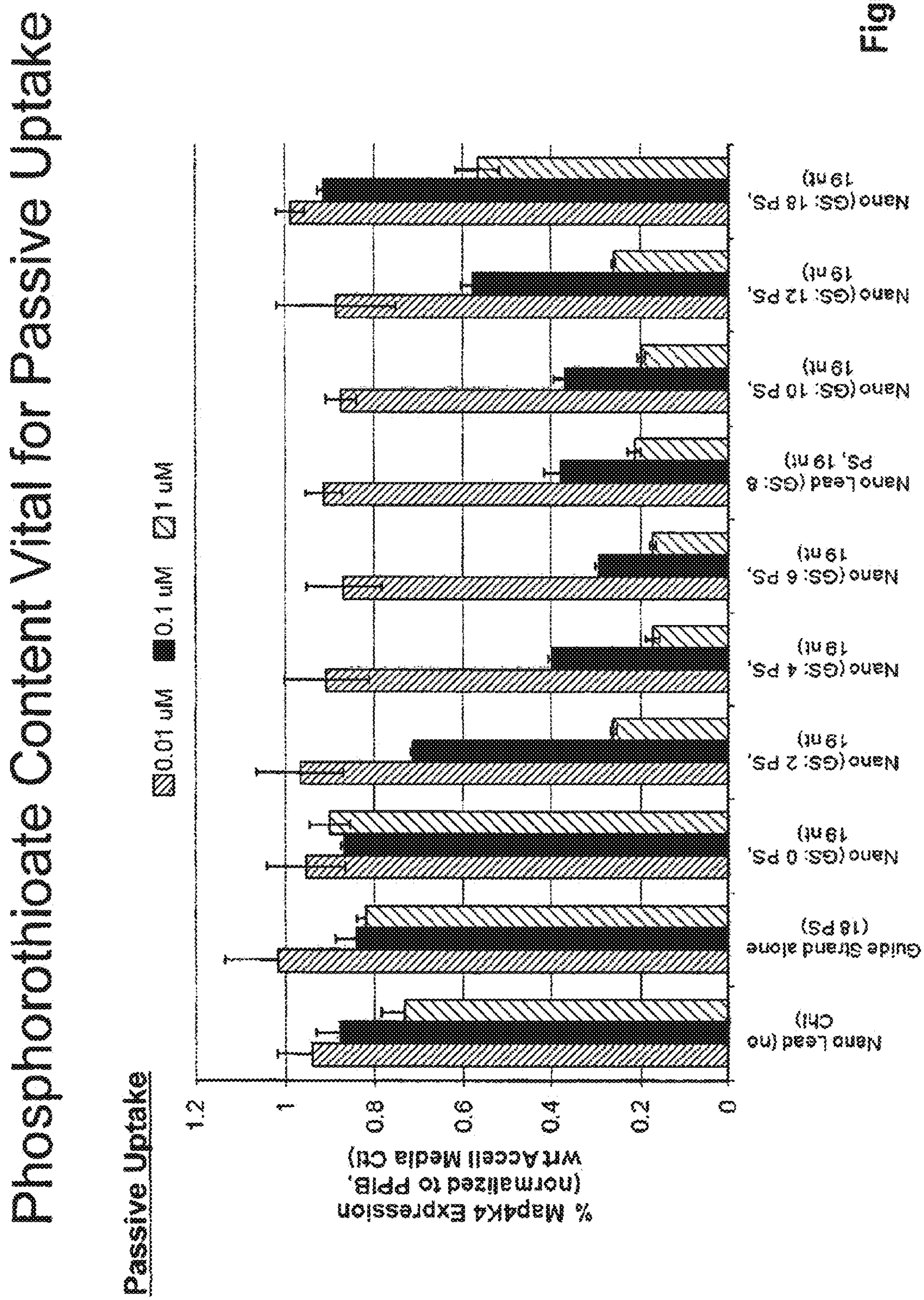

Phosphorothioate Content Vital for Passive Uptake
Passive Uptake (0.1 uM)
% Map4K4 Expression (normalized to PPIB, wrt Accell Media Ctl)
1
0.9
0.8
0.7
0.6
0.5
0.4
0.3
0.2
0.1
0
Nano Lead (no Chl)
Guide Strand alone (18 PS)
Nano (GS: 0 PS, 19 nt)
Nano (GS: 2 PS, 19 nt)
Nano (GS: 4 PS, 19 nt)
Nano (GS: 6 PS, 19 nt)
Nano Lead (GS: 8 PS, 19 nt)
Nano (GS: 10 PS, 19 nt)
Nano (GS: 12 PS, 19 nt)
Nano (GS: 18 PS, 19 nt)

Figure 41



Phosphorothioate Content Vital for Passive Uptake
Passive Uptake
0.01 uM
0.1 uM
1 uM
% Map4K4 Expression (normalized to PPIB, wrt Accell Media Ctl)
1.2
1
0.8
0.6
0.4
0.2
0
Nano Lead (no Chl)
Guide Strand alone (18 PS)
Nano (GS: 0 PS, 19 nt)
Nano (GS: 2 PS, 19 nt)
Nano (GS: 4 PS, 19 nt)
Nano (GS: 6 PS, 19 nt)
Nano Lead (GS: 8 PS, 19 nt)
Nano (GS: 10 PS, 19 nt)
Nano (GS: 12 PS, 19 nt)
Nano (GS: 18 PS, 19 nt)

Figure 42

Figure 43

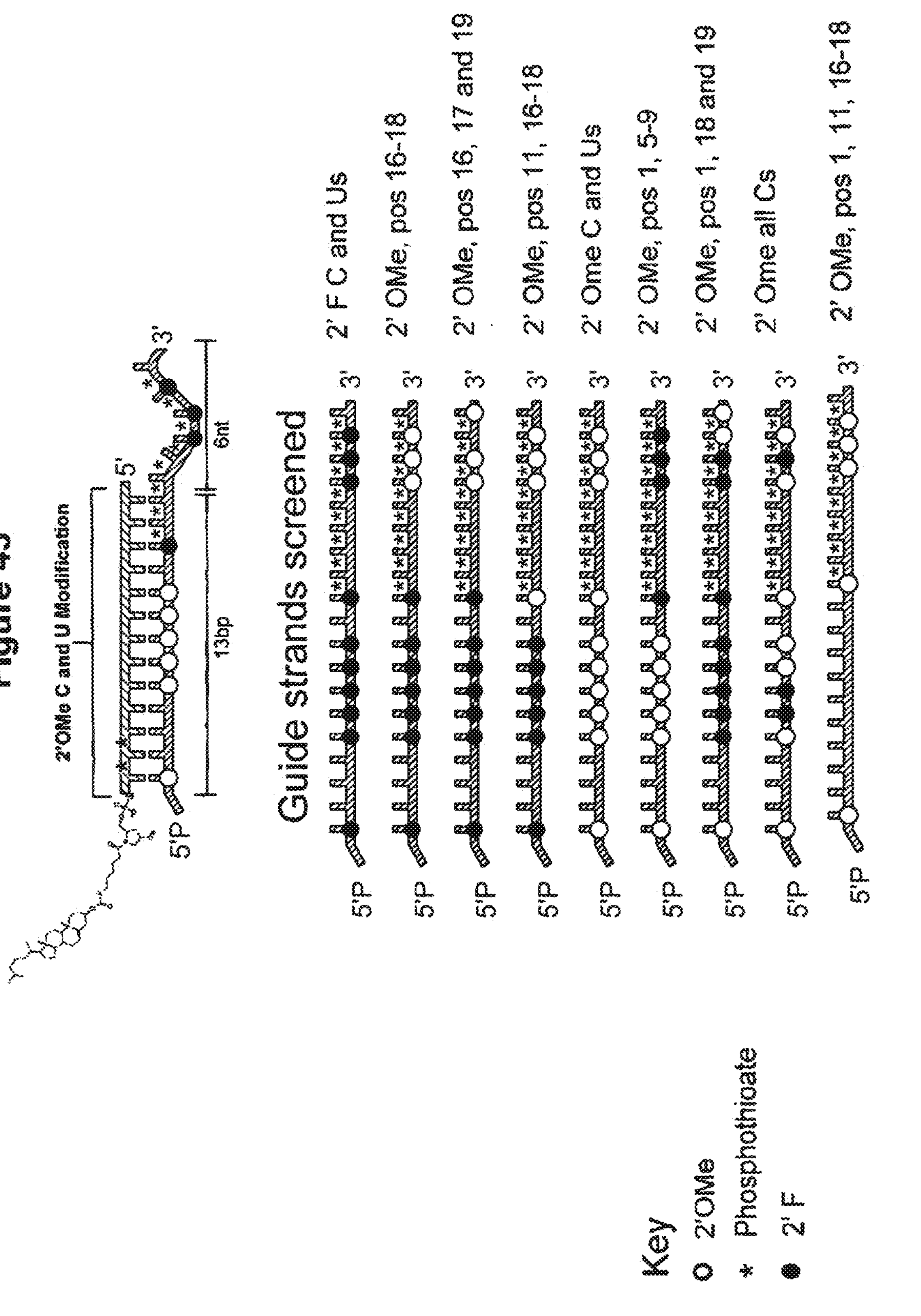

2'OMe C and U Modification
5'
3'
5'P
13bp
6nt
Guide strands screened
5'P 3' 2' F C and Us
5'P 3' 2' OMe, pos 16-18
5'P 3' 2' OMe, pos 16, 17 and 19
5'P 3' 2' OMe, pos 11, 16-18
5'P 3' 2' Ome C and Us
5'P 3' 2' OMe, pos 1, 5-9
5'P 3' 2' OMe, pos 1, 18 and 19
5'P 3' 2' Ome all Cs
5'P 3' 2' OMe, pos 1, 11, 16-18
Key
2'OMe
Phosphothioate
2' F

Figure 44

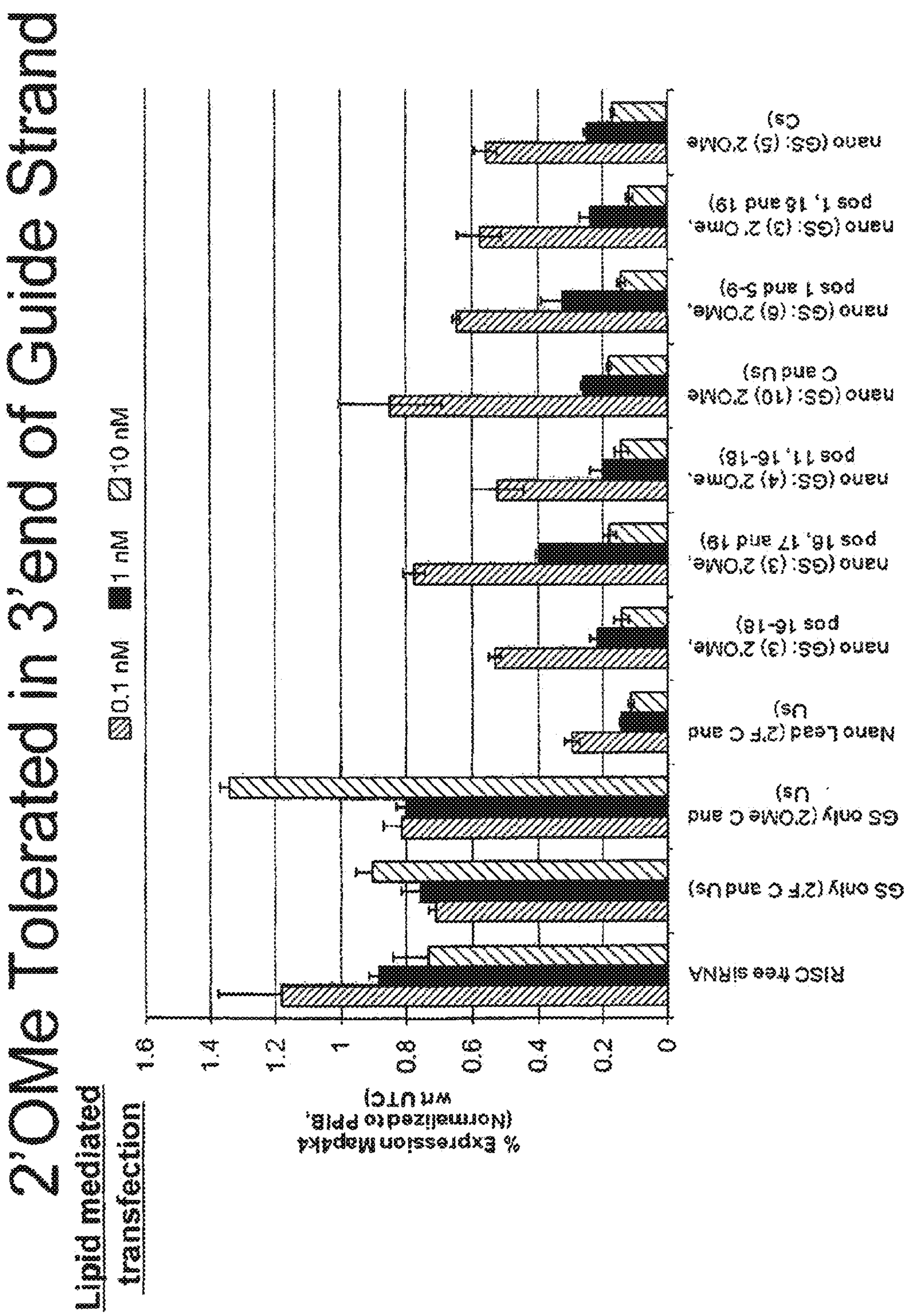

2'OMe Tolerated in 3'end of Guide Strand
Lipid mediated transfection
0.1 nM
1 nM
10 nM
% Expression Mapk4 (Normalized to PPIB, wrt UTC)
0
0.2
0.4
0.6
0.8
1
1.2
1.4
1.6
RISC free siRNA
GS only (2'F C and Us)
GS only (2'OMe C and Us)
Nano Lead (2'F C and Us)
nano (GS: (3) 2'OMe, pos 16-18)
nano (GS: (3) 2'OMe, pos 16, 17 and 19)
nano (GS: (4) 2'OMe, pos 11, 16-18)
nano (GS: (10) 2'OMe C and Us)
nano (GS: (6) 2'OMe, pos 1 and 5-9)
nano (GS: (3) 2' Ome, pos 1, 18 and 19)
nano (GS: (5) 2'OMe Cs)

Figure 45

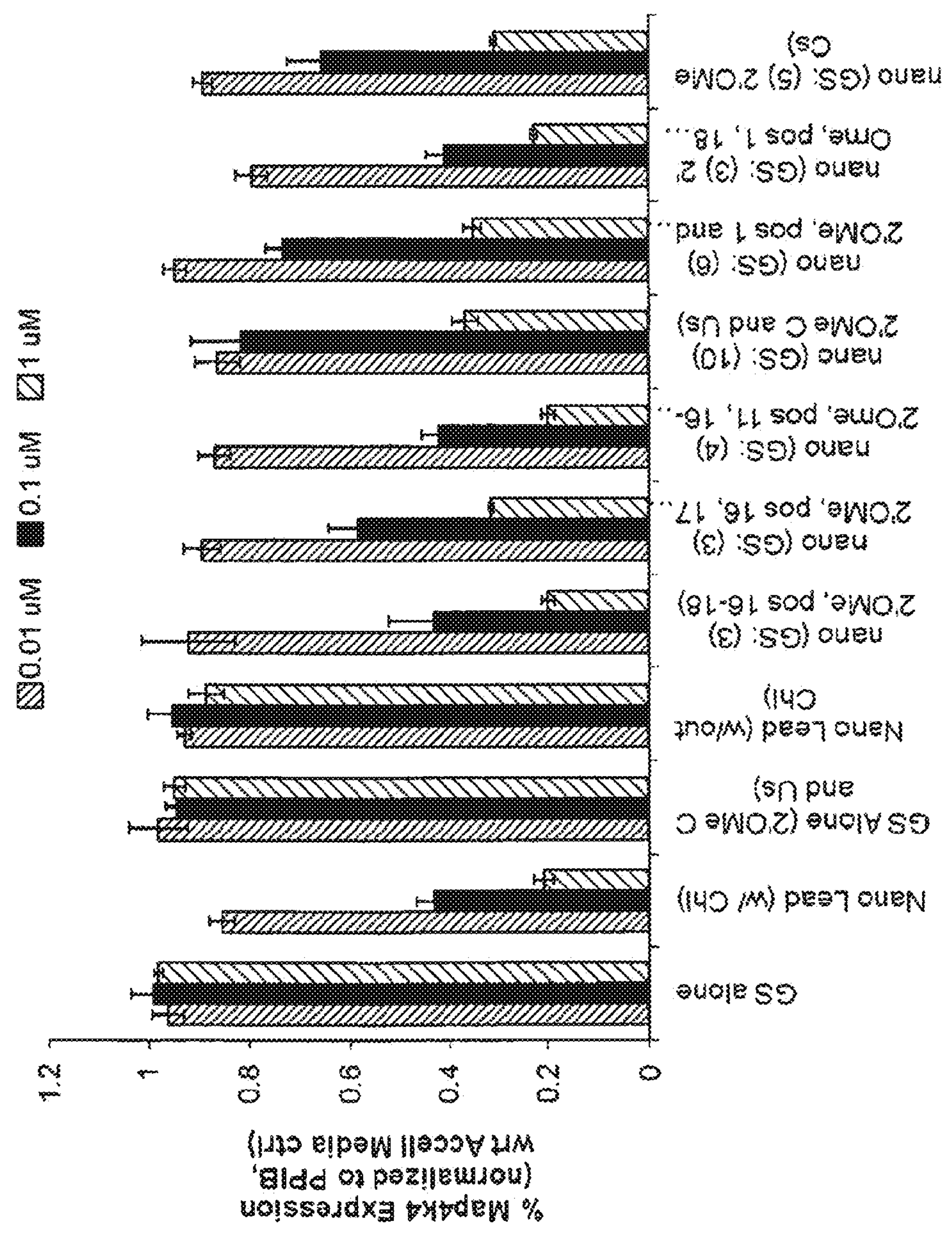

0.01 uM
0.1 uM
1 uM
% Mapk4 Expression (normalized to PPIB, wrt Accell Media ctrl)
0
0.2
0.4
0.6
0.8
1
1.2
GS alone
Nano Lead (w/ Chl)
GS Alone (2'OMe C and Us)
Nano Lead (w/out Chl)
nano (GS: (3) 2'OMe, pos 16-18)
nano (GS: (3) 2'OMe, pos 16, 17...
nano (GS: (4) 2'Ome, pos 11, 16-...
nano (GS: (10) 2'OMe C and Us)
nano (GS: (6) 2'OMe, pos 1 and...
nano (GS: (3) 2' Ome, pos 1, 18...
nano (GS: (5) 2'OMe Cs)

Figure 46

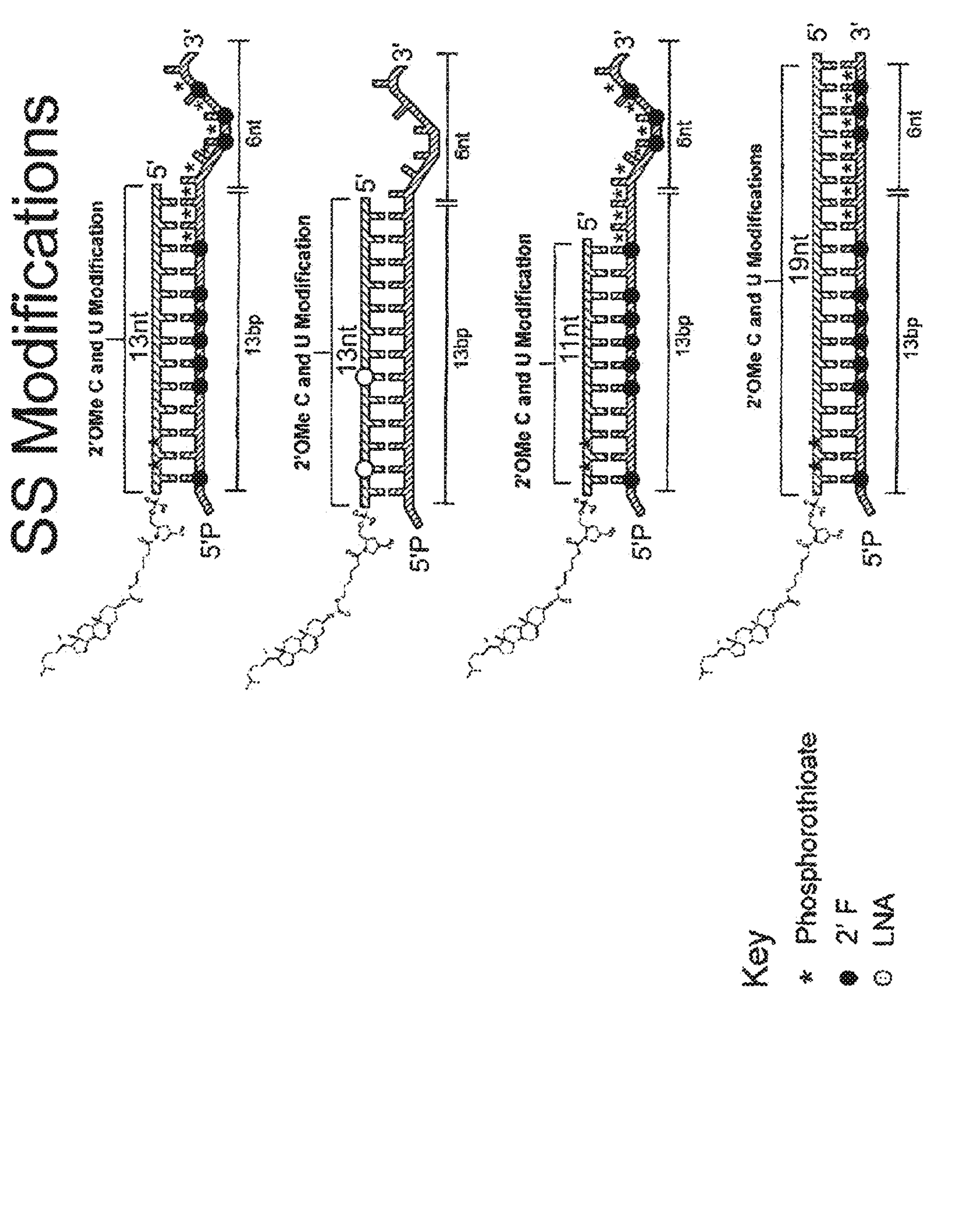
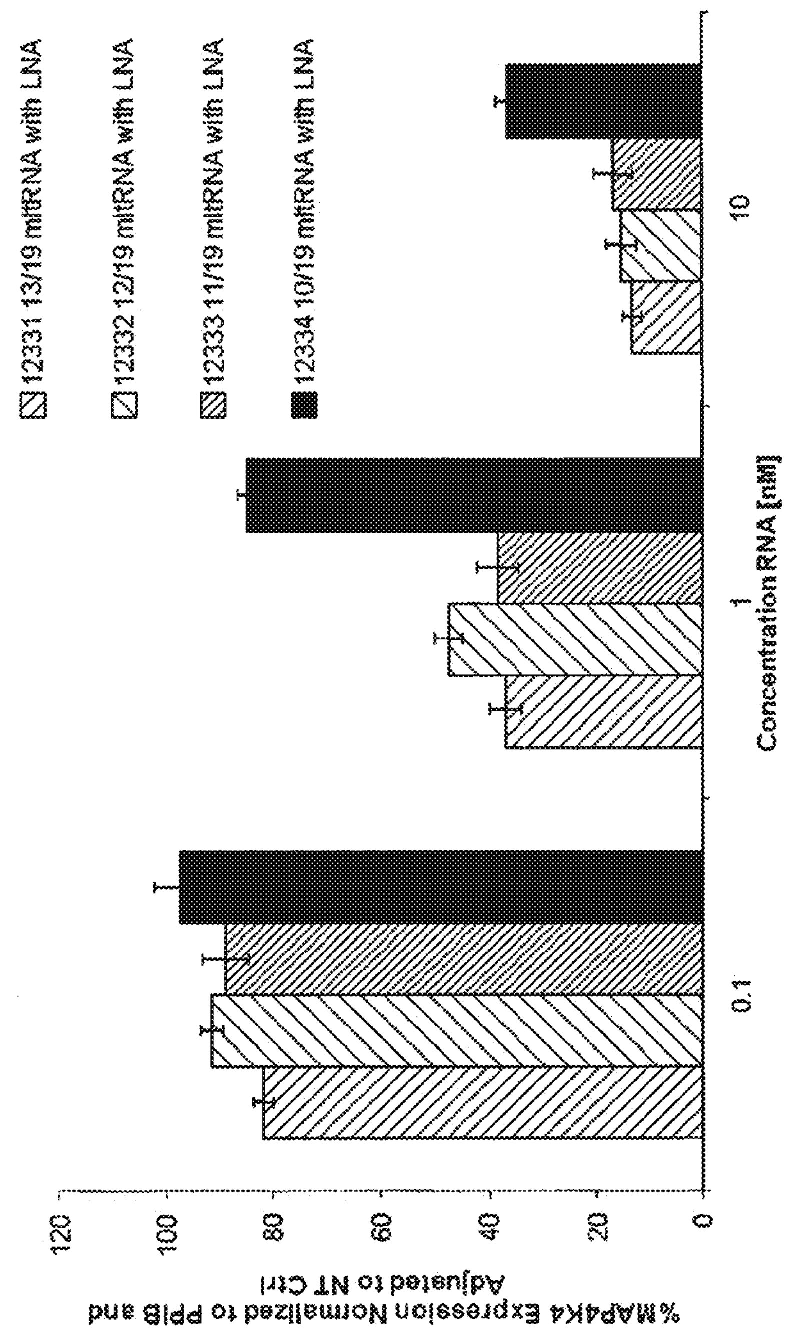

SS Modifications
2'OMe C and U Modification
13nt
5'
3'
5'P
13bp
6nt
2'OMe C and U Modification
13nt
5'
3'
5'P
13bp
6nt
2'OMe C and U Modification
11nt
5'
3'
5'P
13bp
6nt
2'OMe C and U Modifications
19nt
5'
3'
5'P
13bp
6nt
Key
* Phosphorothioate
● 2' F
○ LNA

Figure 47

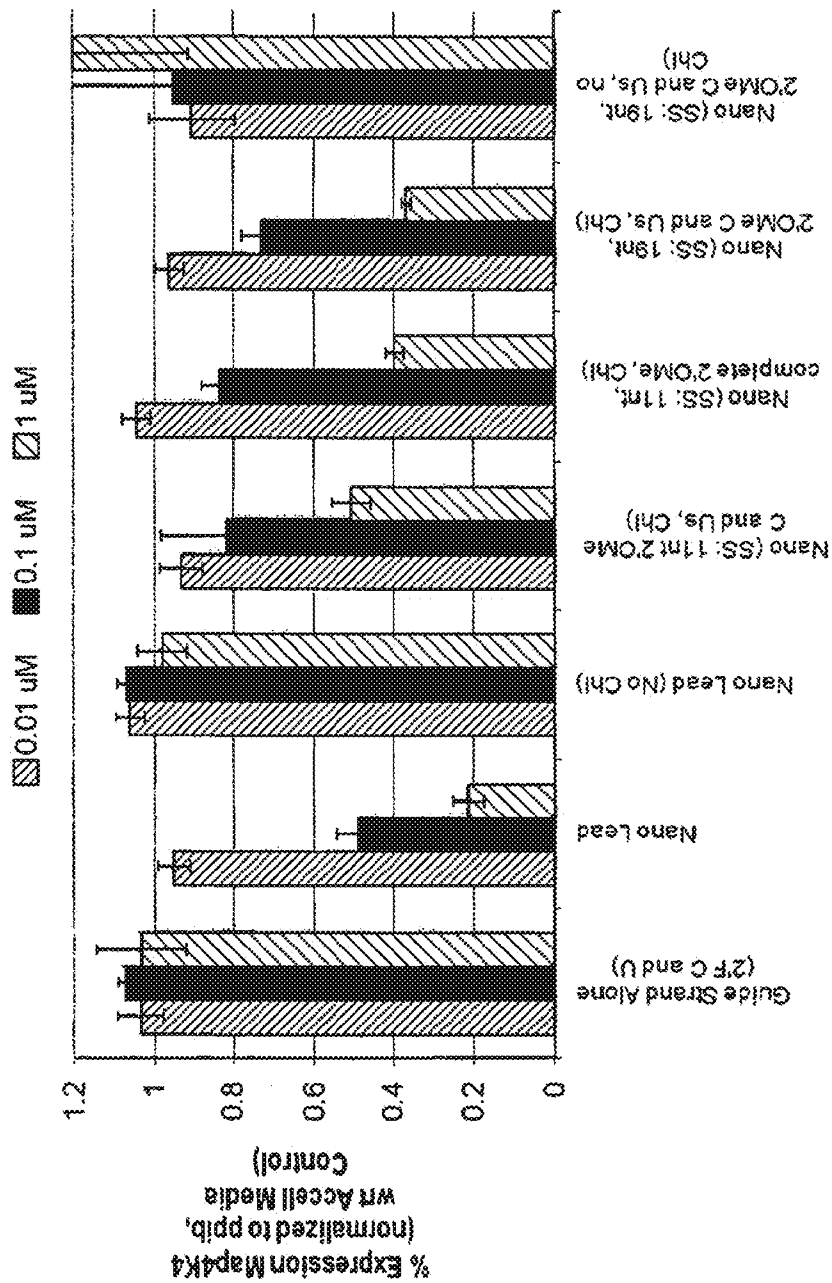


12331 13/19 mitRNA with LNA
12332 12/19 mitRNA with LNA
12333 11/19 mitRNA with LNA
12334 10/19 mitRNA with LNA
%MAP4K4 Expression Normalized to PPIB and Adjusted to NT Ctrl
120
100
80
60
40
20
0
0.1
1
10
Concentration RNA [nM]

Figure 48

13 Bases Optimal Length in Sense Strand

Passive Uptake



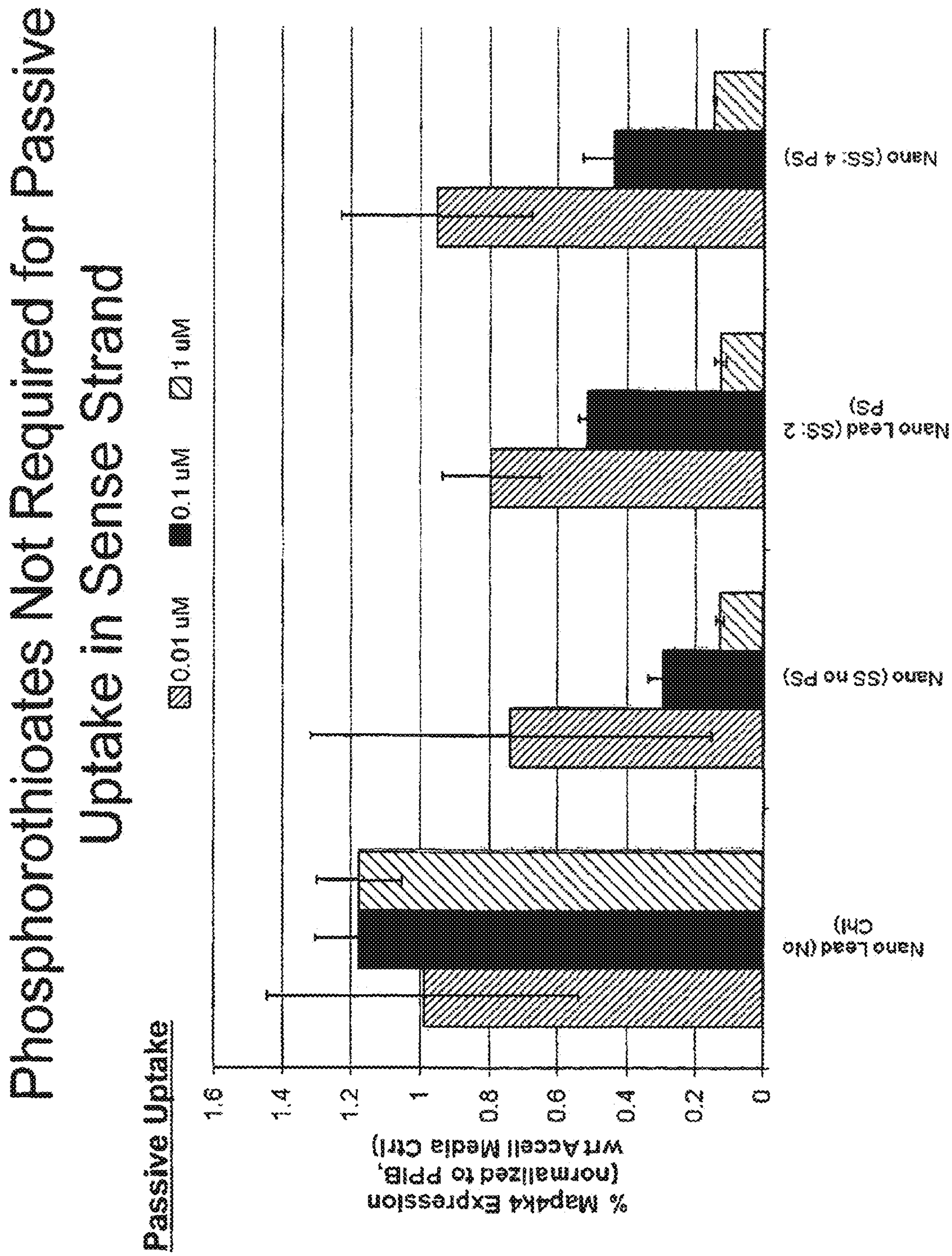
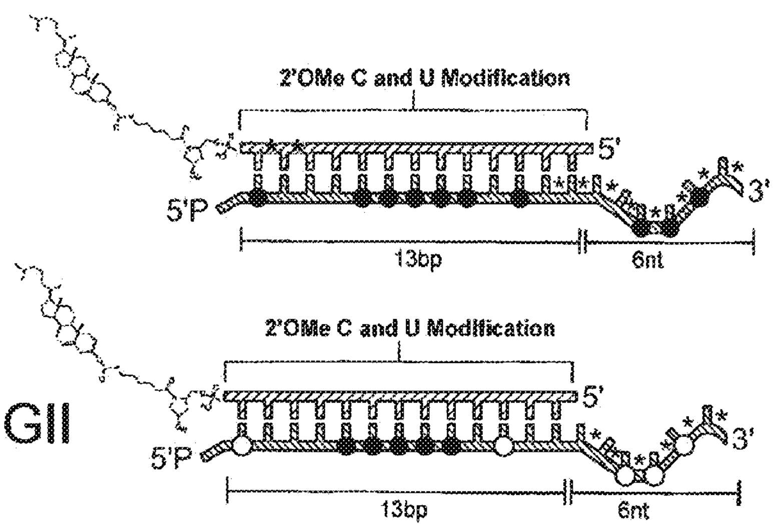

Passive Uptake
Phosphorothioates Not Required for Passive Uptake in Sense Strand
0.01 uM
0.1 uM
1 uM
% Mapk4 Expression (normalized to PPIB, wrt Accell Media Ctrl)
1.6
1.4
1.2
1
0.8
0.6
0.4
0.2
0
Nano Lead (No Chl)
Nano (SS no PS)
Nano Lead (SS: 2 PS)
Nano (SS: 4 PS)

Figure 49

Figure 50

2nd Generation sd-rxRNA^{nano} Lead



sd-rxRNA^{nano} GII

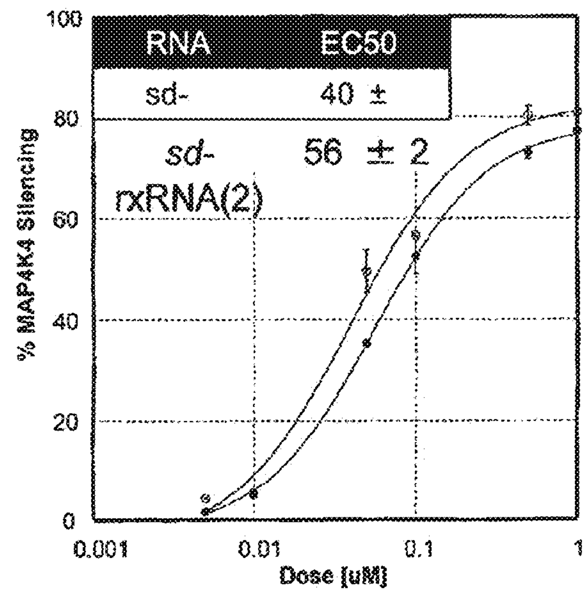
- 40 % reduction in PS content
- 40-50% reduction in 2'F content

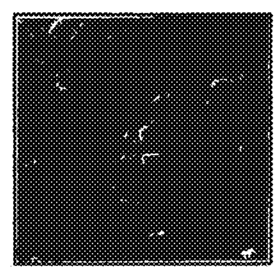
Key
o 2'OMe
* Phosphothioate
● 2' F

Figure 51

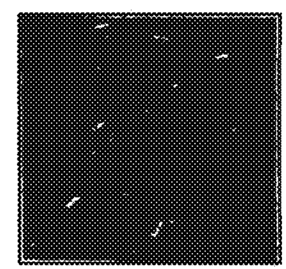
sd-rxRNA™: Spontaneous Cellular Uptake and Efficacy Without Delivery Vehicle

- Chemically modified bipartite RNAi molecules with self-delivering moiety(s)
- *Picomolar* activity after facilitated delivery(lipid-mediated transfection)
- *Nanomolar* activity in cell culture with NO transfection reagent **(self-delivery)**
- Efficient uptake (>95%) by most cell types in cell culture
- Stable (more then 3 days in 100% human serum)
- Results in distribution to tissues; reduced kidney clearance
- Compatible with SC administration
- Highly specific (little or no immune induction)





DY547-labeled rxRNA^{ori} + Hoechst nuclear staining



DY547-labeled *sd*-rxRNA + Hoechst nuclear staining

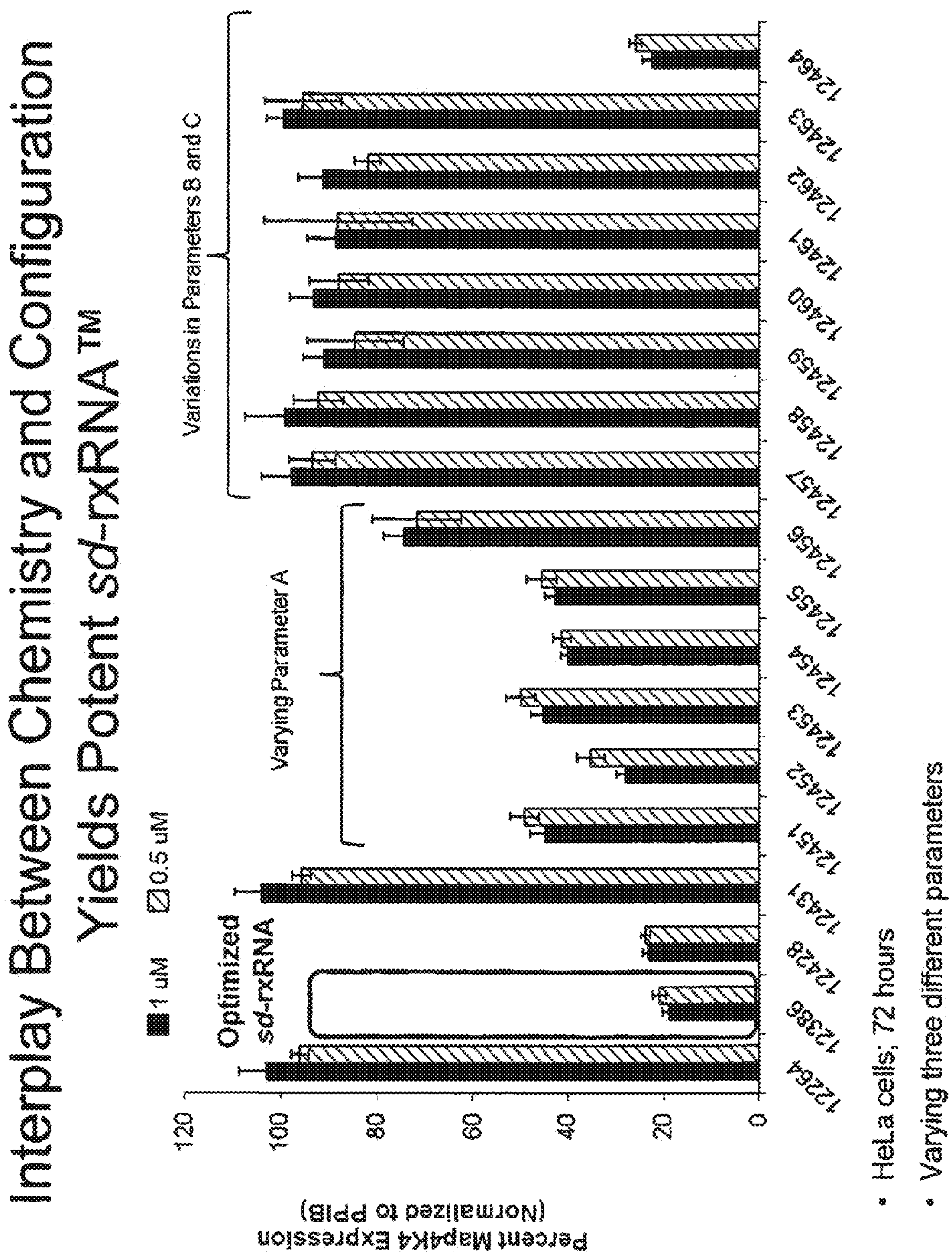

Interplay Between Chemistry and Configuration
Yields Potent sd-rxRNA™
1 uM
0.5 uM
Optimized
sd-rxRNA
Varying Parameter A
Variations in Parameters B and C
Percent Map4K4 Expression
(Normalized to PPIB)
120
100
80
60
40
20
0
12264
12386
12428
12431
12451
12452
12453
12454
12455
12456
12457
12458
12459
12460
12461
12462
12463
12464
• HeLa cells; 72 hours
• Varying three different parameters

Figure 52

Figure 53

Chemistry Type and Content is Essential for sd-rxRNA ™ Efficacy

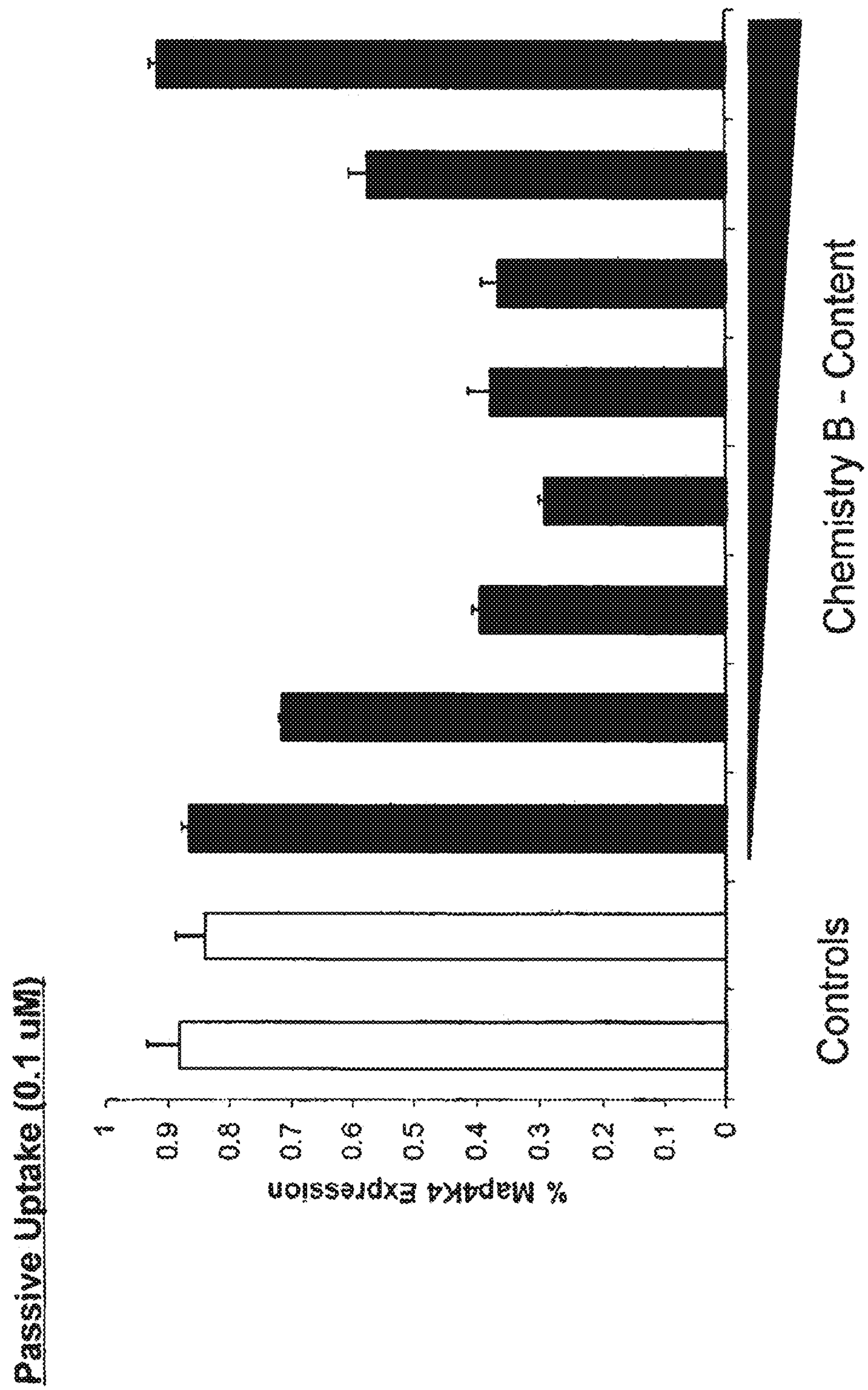
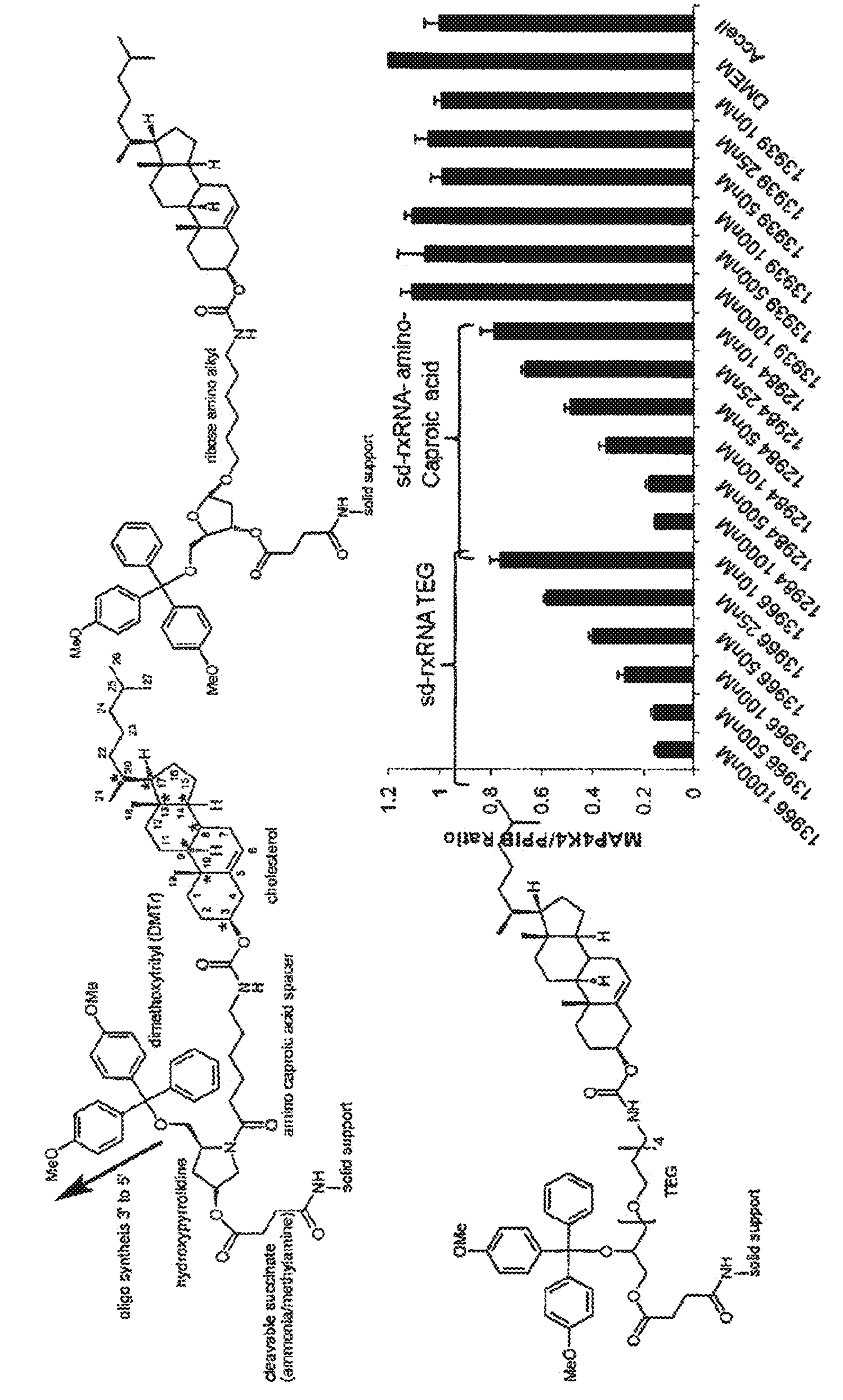


Figure 54



oligo synthesis 3' to 5'
hydroxyprolinol
cleavable succinate
(ammonia/methylamine)
solid support
amino caproic acid spacer
dimethoxytrityl (DMTr)
cholesterol
ribose amino alkyl
TEG
sd-rxRNA TEG
sd-rxRNA- amino-
Caproic acid
MAP4K4/PPIB Ratio
13966 1000nM
13966 500nM
13966 100nM
13966 50nM
13966 25nM
13966 10nM
12984 1000nM
12984 500nM
12984 100nM
12984 50nM
12984 25nM
12984 10nM
13939 1000nM
13939 500nM
13939 100nM
13939 50nM
13939 25nM
13939 10nM
DMEM
Accell

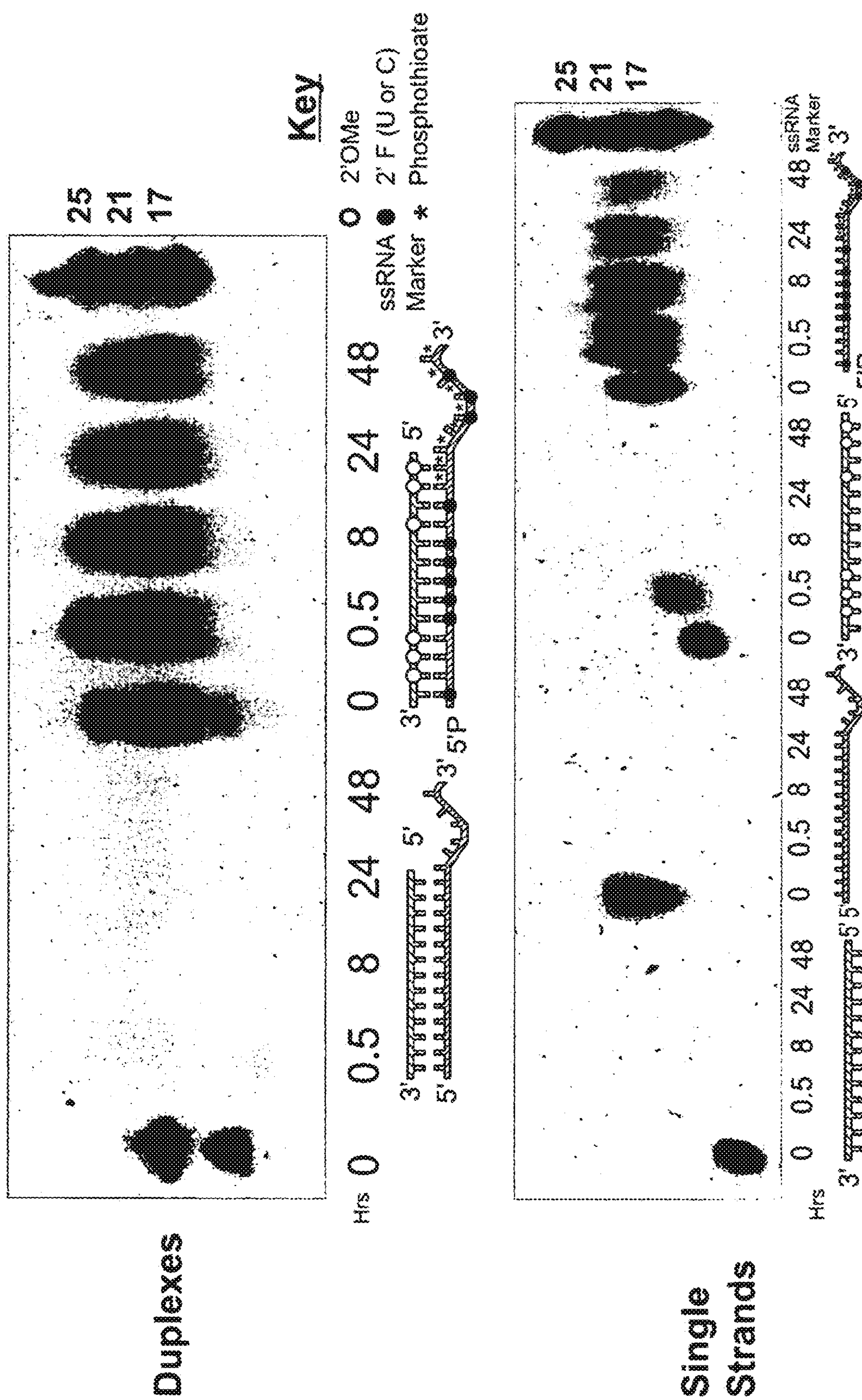
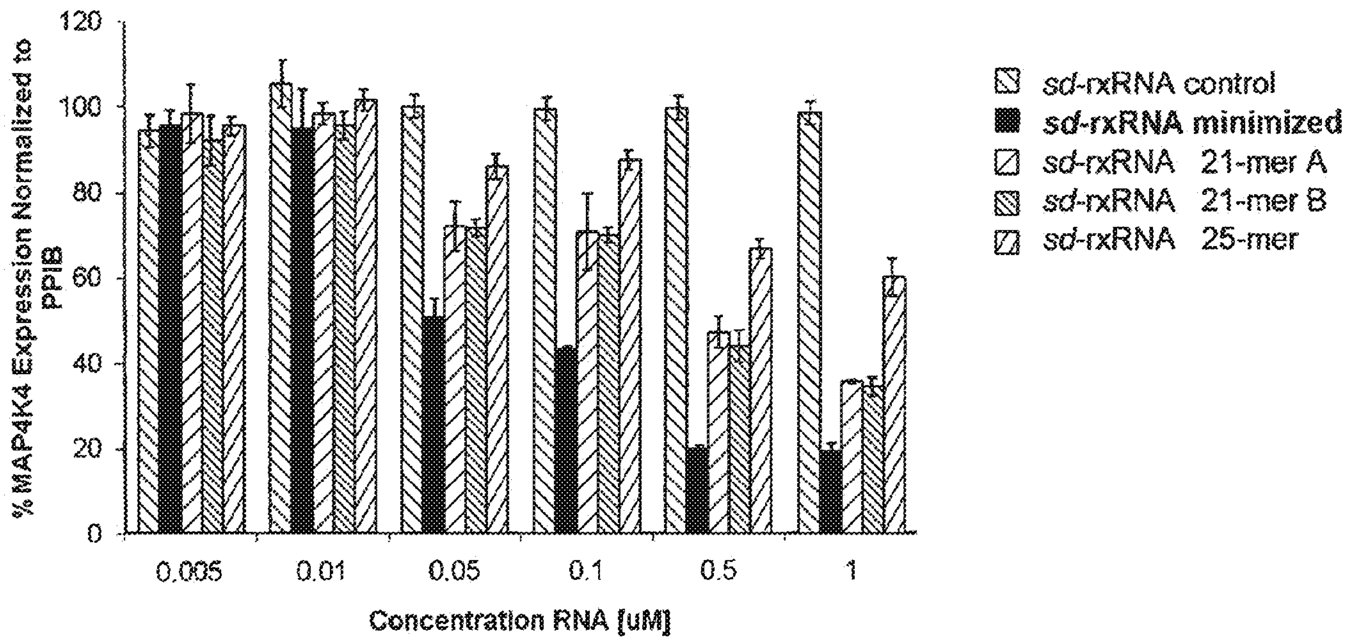

Duplexes
Single Strands
Key
2'OMe
2' F (U or C)
Phosphothioate
25
21
17
Hrs
ssRNA Marker

Figure 55

Figure 56

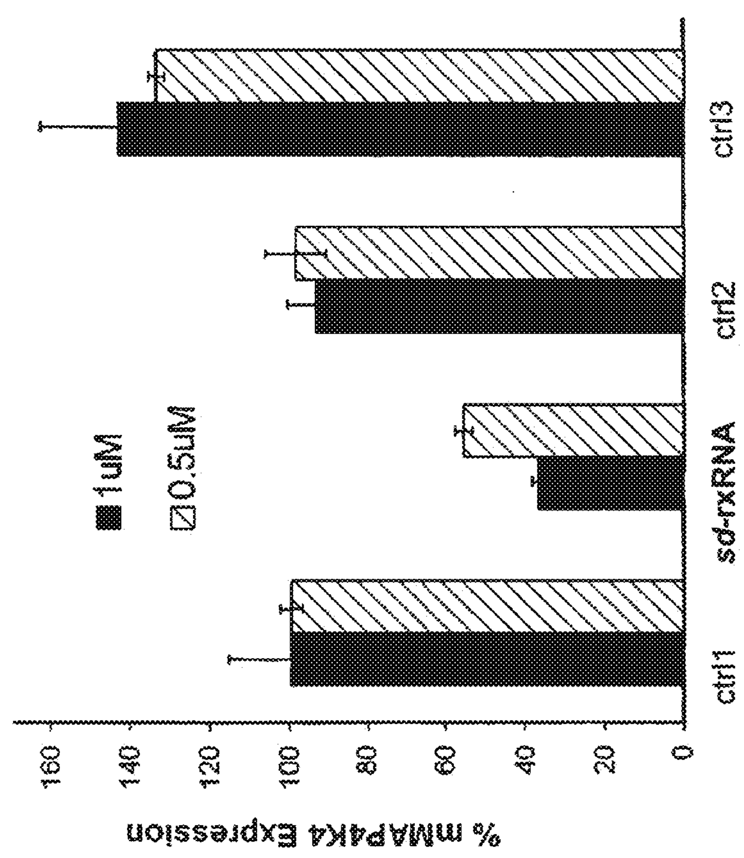
sd-rxRNA™: Minimizing Oligonucleotide Content is Important for Cellular Uptake

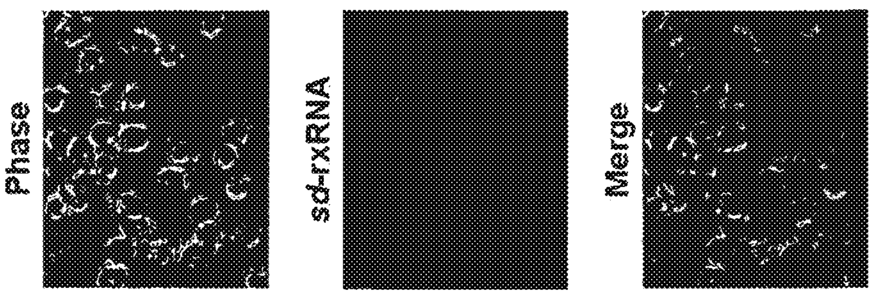


- Spontaneous cellular uptake (HeLa)
- Lead ***sd*-rxRNA** compound is based on **rxRNA**^{nano}
- Minimizing oligonucleotide content is critical for efficient uptake

Figure 57

sd-rxRNA™: Spontaneous Uptake and Target Gene Silencing in Primary Cells

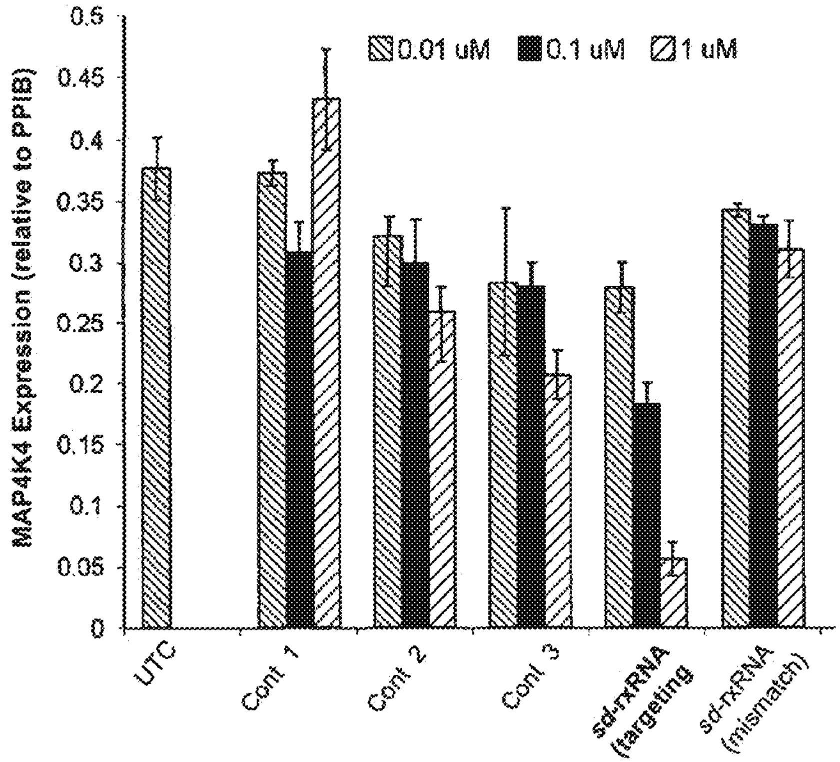


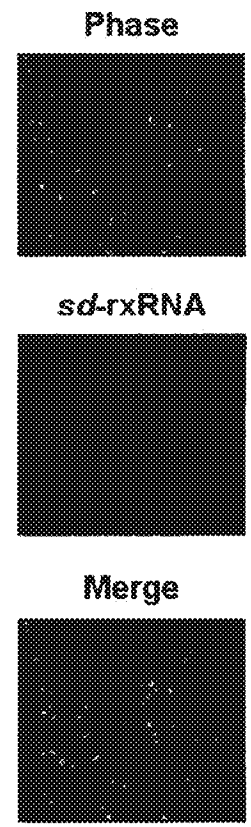


- Target silencing after spontaneous cellular uptake in mouse PEC-derived macrophages

Figure 58

sd-rxRNA™: Spontaneous Uptake and Target Gene Silencing in Primary Cells

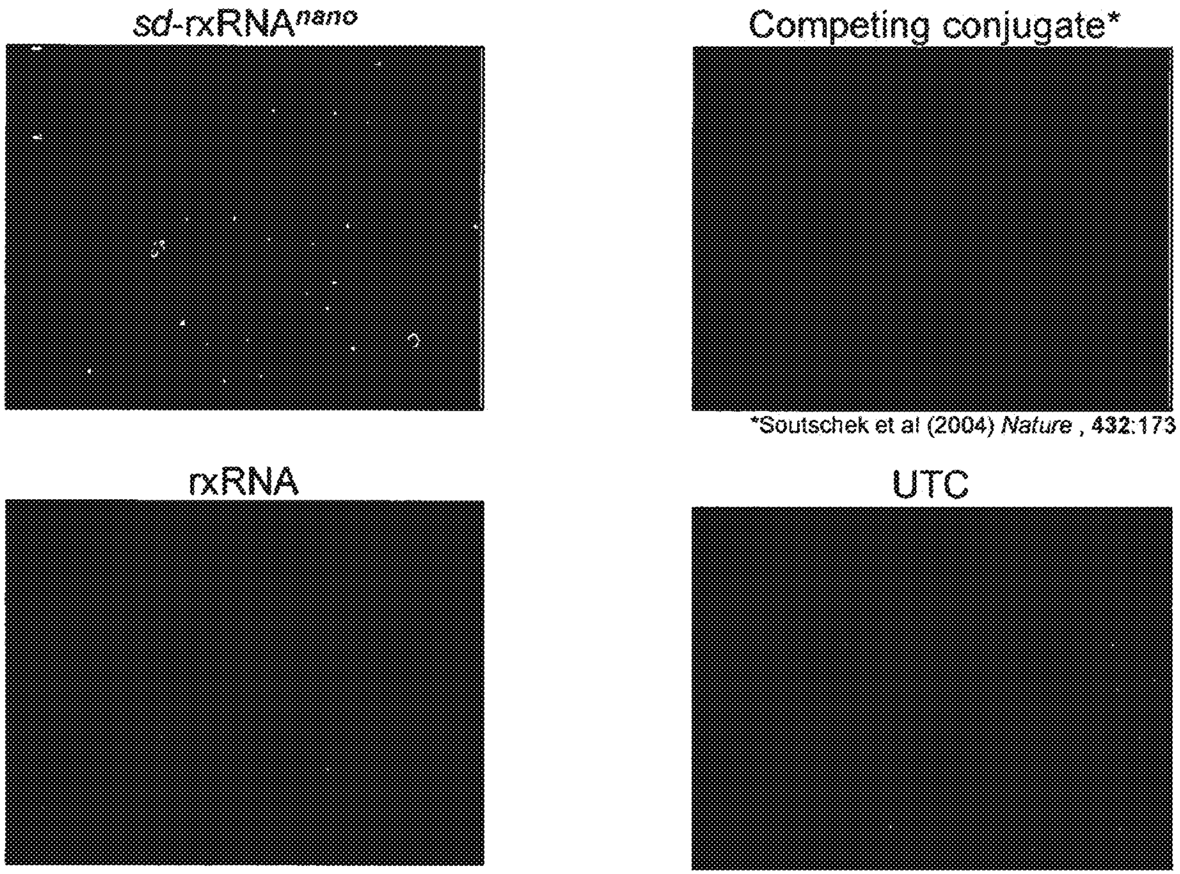




- Target knockdown after spontaneous cellular uptake in mouse primary hepatocytes

Figure 59

sd-rxRNA Delivery to RPE Cells With No Formulation



*Soutschek et al (2004) *Nature* , 432:173

- DY547 and Hoechst
- 24 hr exposure
- 0.5 uM RNA
- No Formulation
- A-RPE 19 Cells

Figure 60

Silencing of MAP4K4 in RPE Cells Treated with *sd*-rxRNA^{nano}

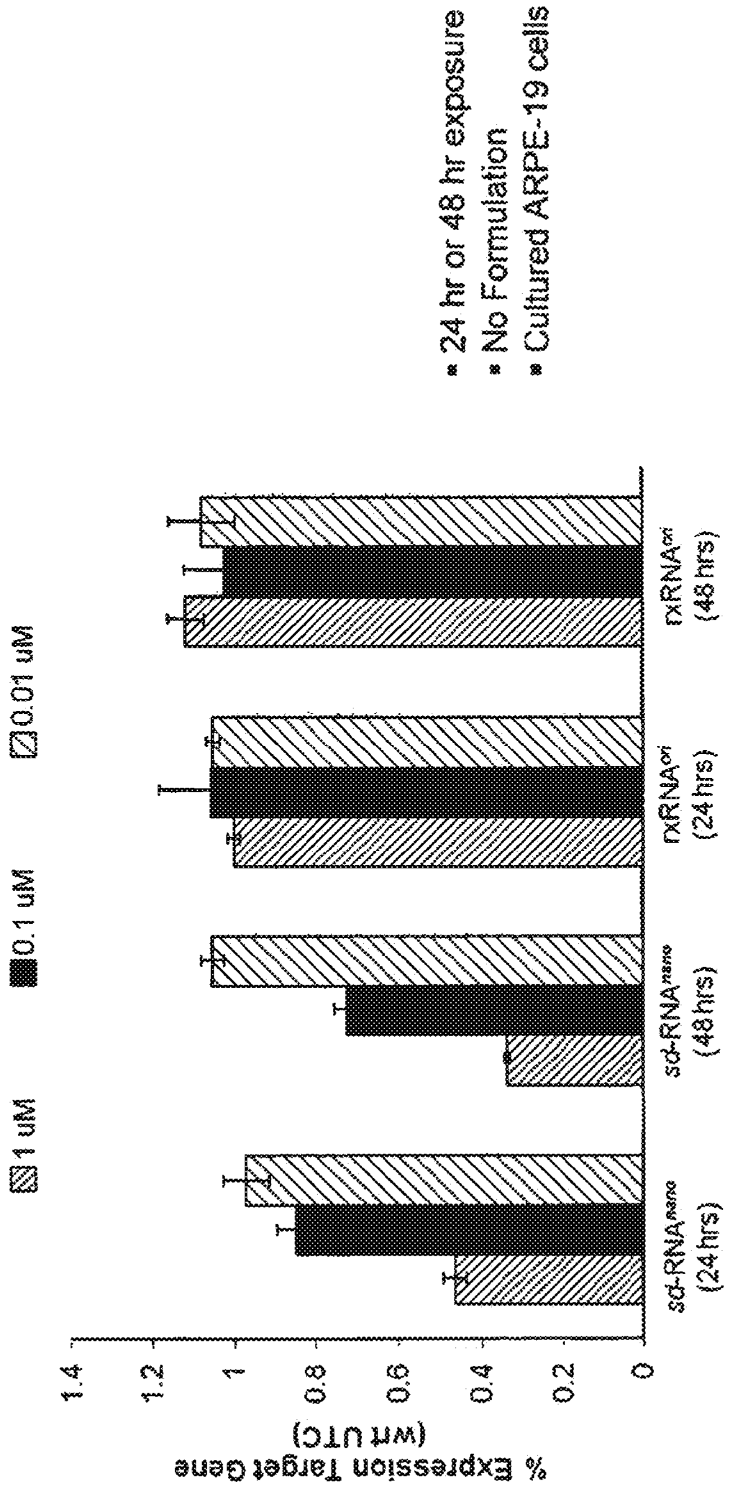
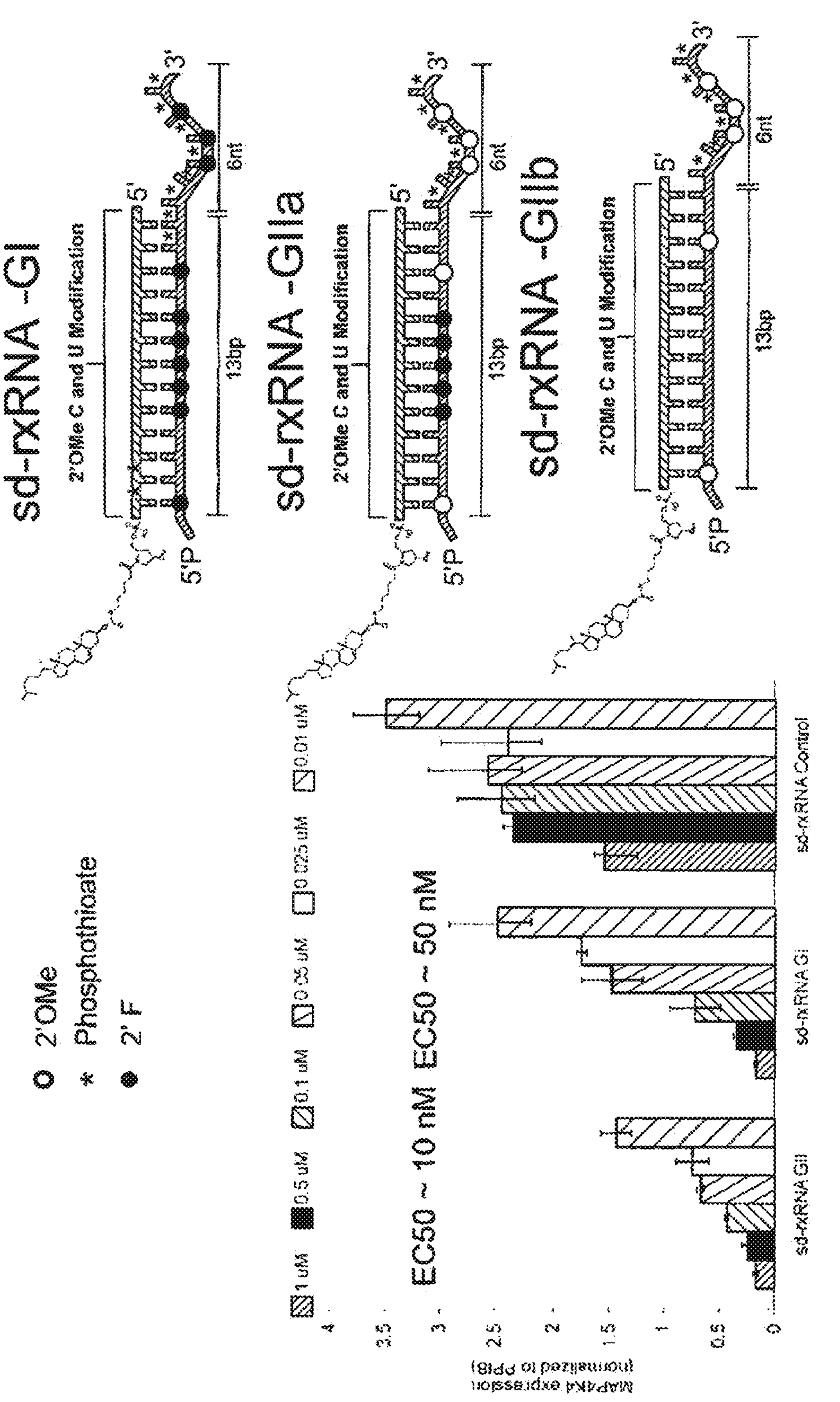
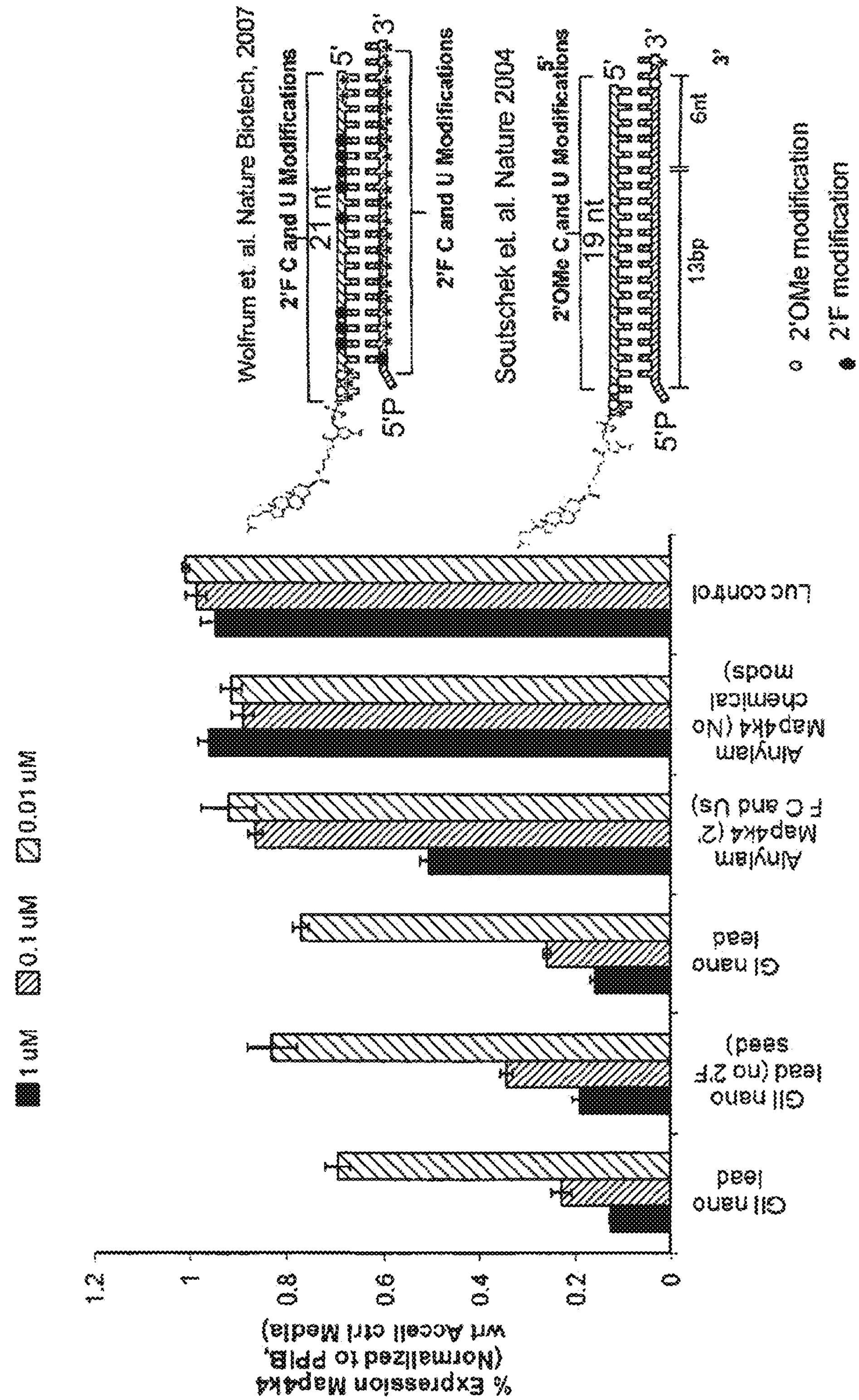


Figure 61



o 2'OMe
* Phosphothioate
● 2' F
sd-rxRNA -GI
sd-rxRNA -GIIa
sd-rxRNA -GIIb
2'OMe C and U Modification
5'
3'
5'P
13bp
6nt
EC50 ~ 10 nM EC50 ~ 50 nM
1 uM
0.5 uM
0.1 uM
0.05 uM
0.025 uM
0.01 uM
MAP4K4 expression (normalized to PPIB)
0
0.5
1
1.5
2
2.5
3
3.5
4
sd-rxRNA GII
sd-rxRNA GI
sd-rxRNA Control

Figure 62



Wolfrum et. al. Nature Biotech, 2007
2'F C and U Modifications
21 nt
5'
3'
5'P
2'F C and U Modifications
Soutschek et. al. Nature 2004
2'OMe C and U Modifications
19 nt
5'
3'
5'P
13bp
6nt
2'OMe modification
2'F modification
1 uM
0.1 uM
0.01 uM
% Expression Map4k4 (Normalized to PPIB, wrt Accell ctrl Media)
1.2
1
0.8
0.6
0.4
0.2
0
Gll nano lead
Gll nano lead (no 2'F seed)
Gl nano lead
Alnylam Map4k4 (2' F C and Us)
Alnylam Map4k4 (No chemical mods)
Luc control

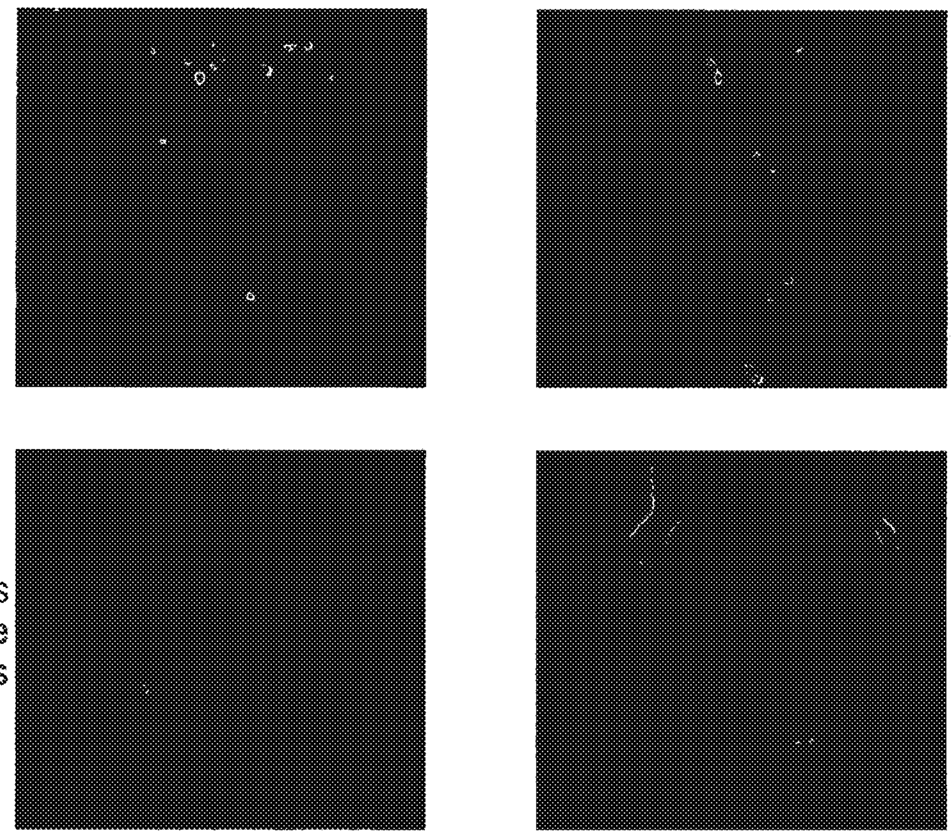
Figure 63

sd-rxRNA™ Is Efficiently Delivered to Cytoplasm

Outside plane | Inside plane

sd-rxRNA™ accumulate inside the cells

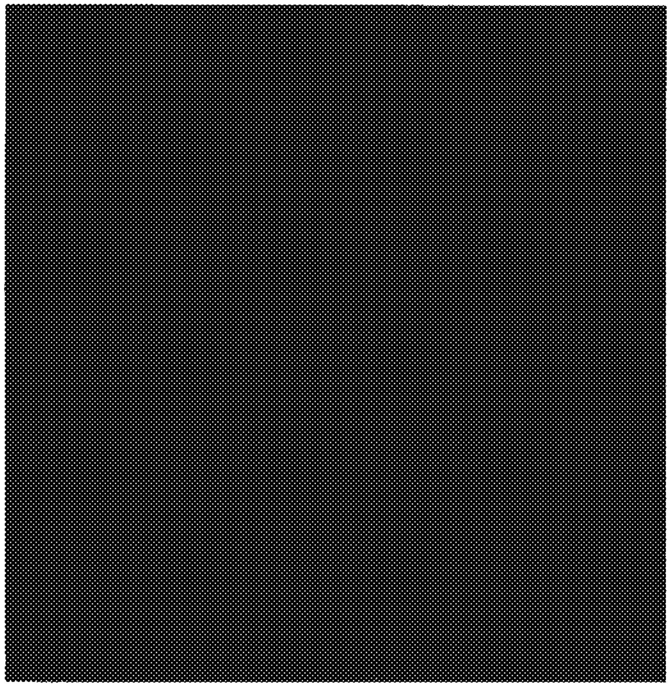
Competing conjugate* RNAs accumulate on the surface of the cells



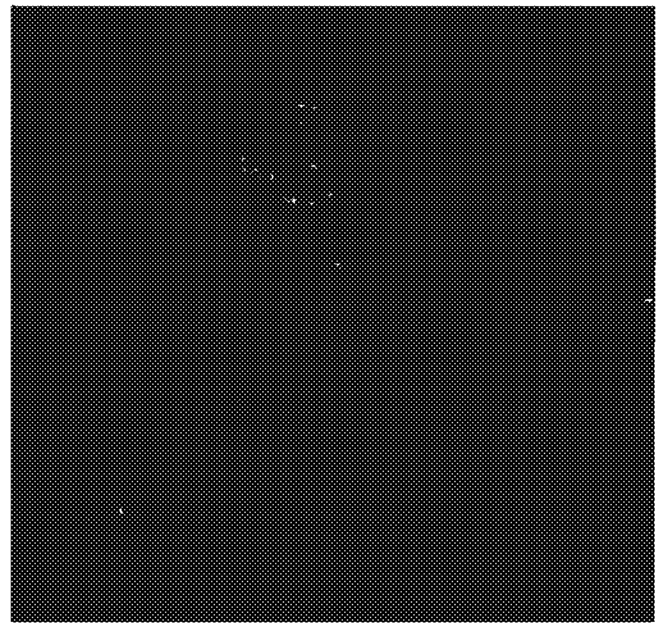
*Soutschek et al (2004) *Nature* , 432:173

Figure 64

sd-rxRNA™ but not Competitor Molecules Are Internalized within Minutes



Competing conjugate* RNAs
*Soutschek et al (2004) *Nature* , 432:173

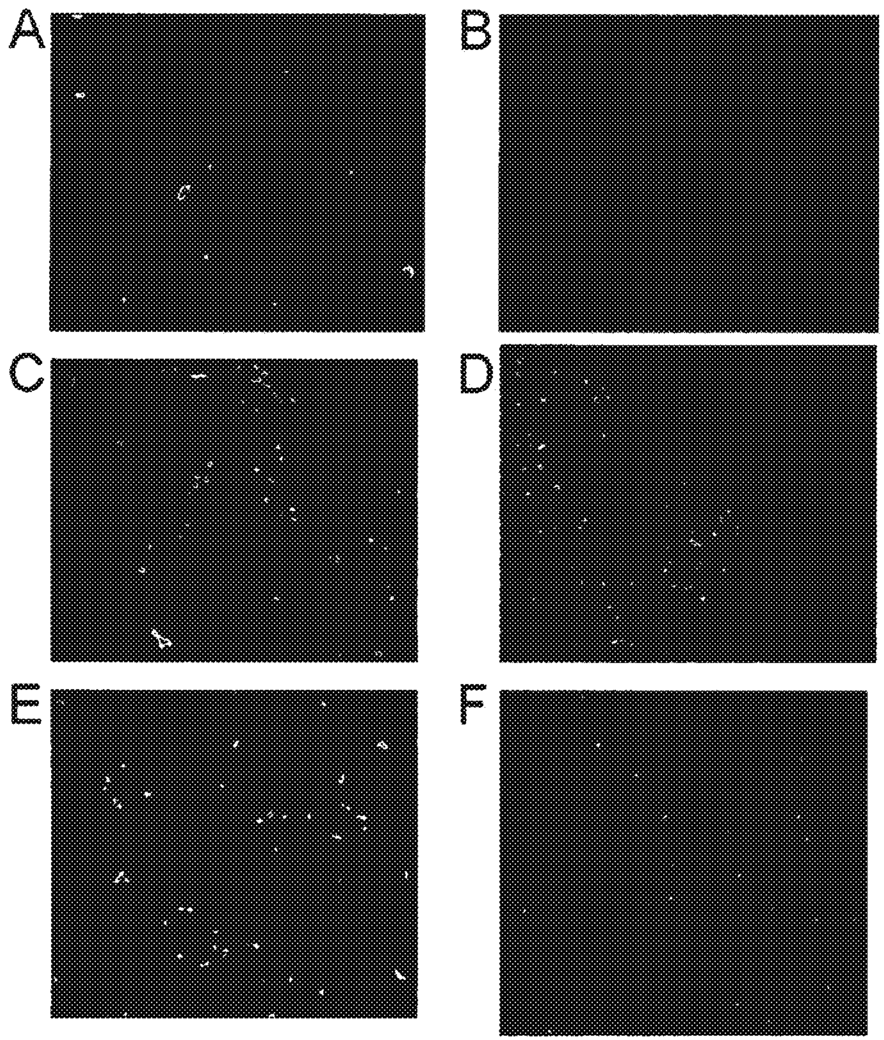


sd-rxRNA™

< 5 minutes exposure (HeLa cells)

Sd-rxRNA GII

Regular siRNA-cholesterol (Soucheck et al 2004)



Tissue Culture
RPE cells (0.5 uM)

Local delivery to
compromised skin
10 ul (1mM solution)

Systemic delivery
(50 mg/ kg IV)
Liver Uptake

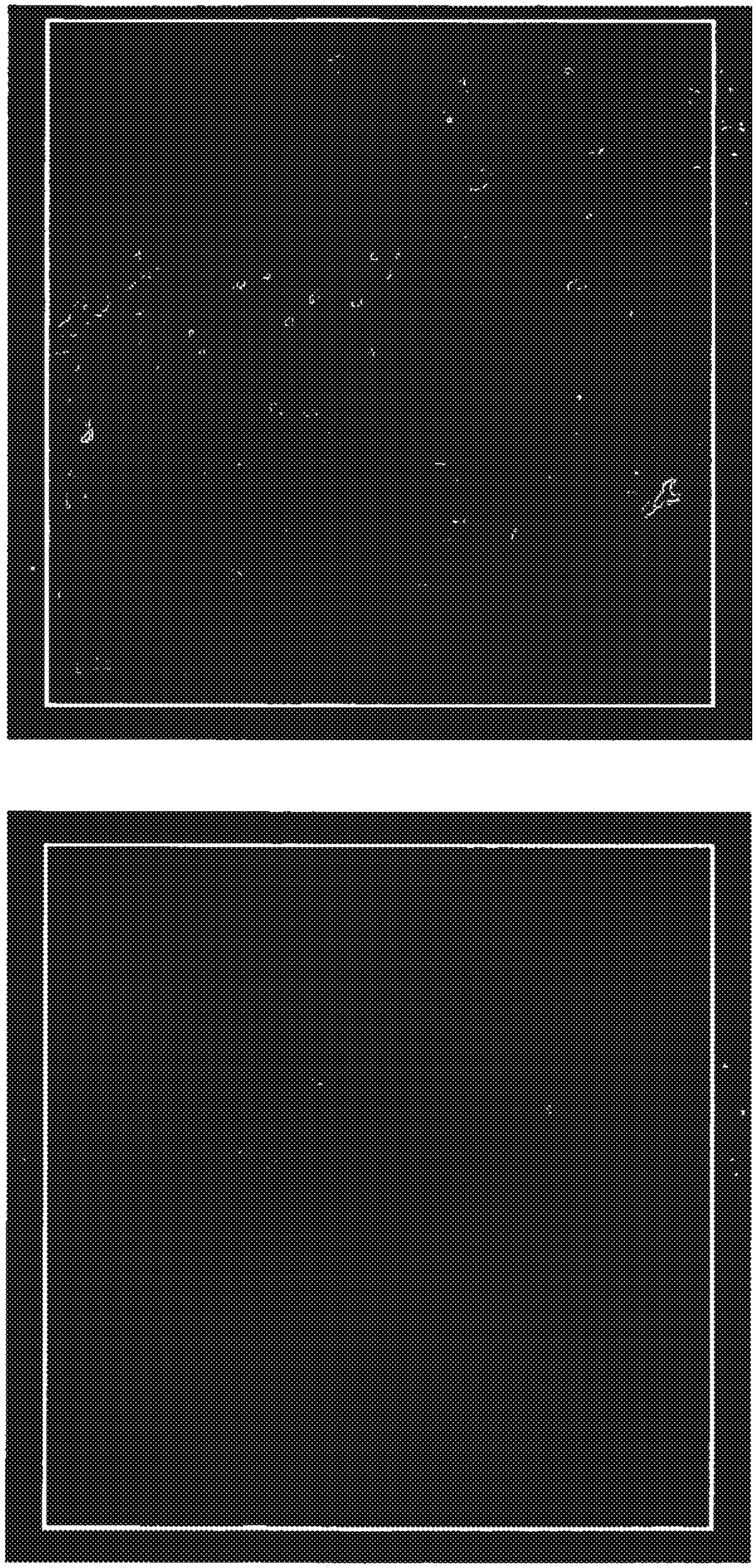
Figure 65

Figure 66

Local Delivery of *sd*-rxRNA™: Pilot Study

rxRNA^{ori}

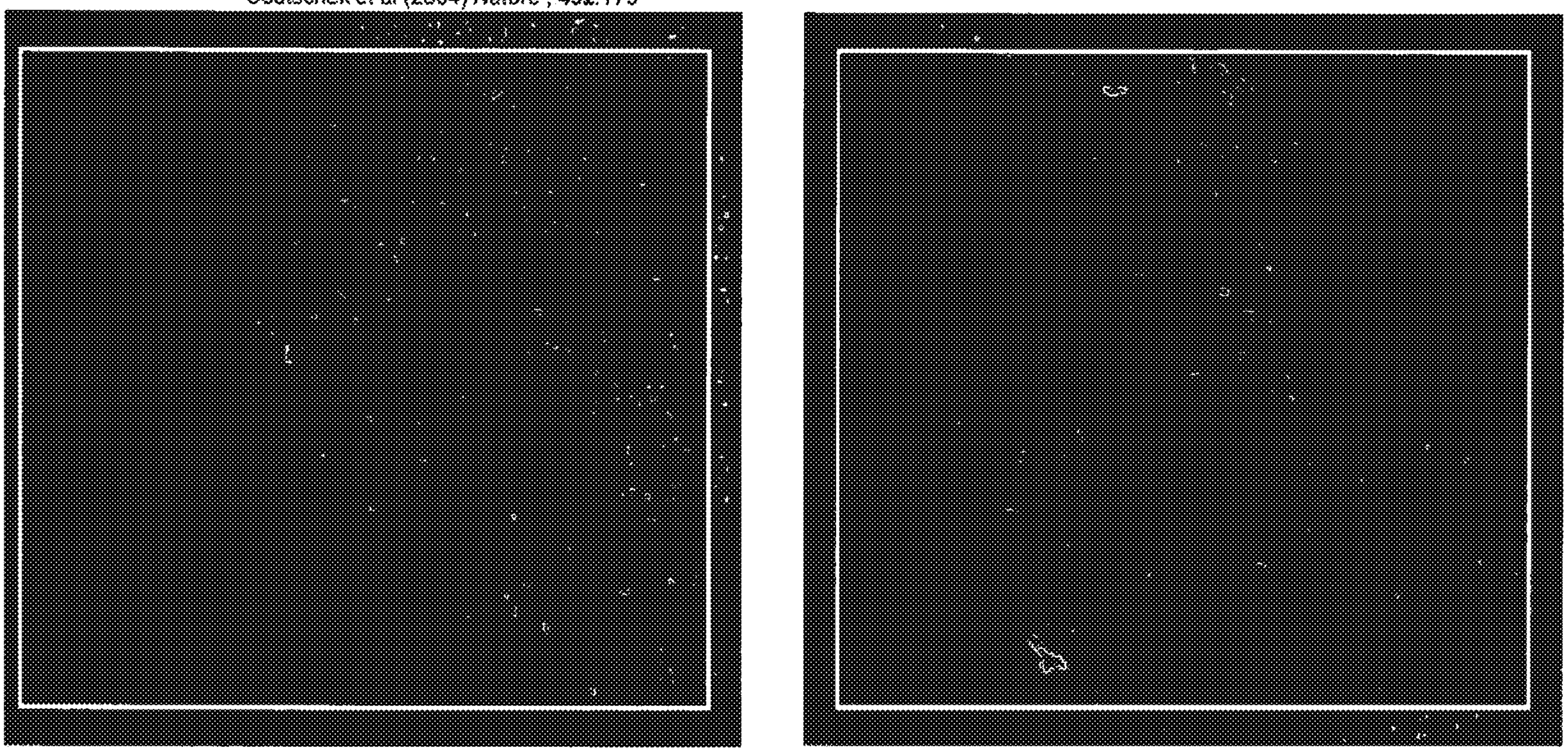
sd-rxRNA™



- 24 hours post delivery
- Hoechst and DY547

Figure 67

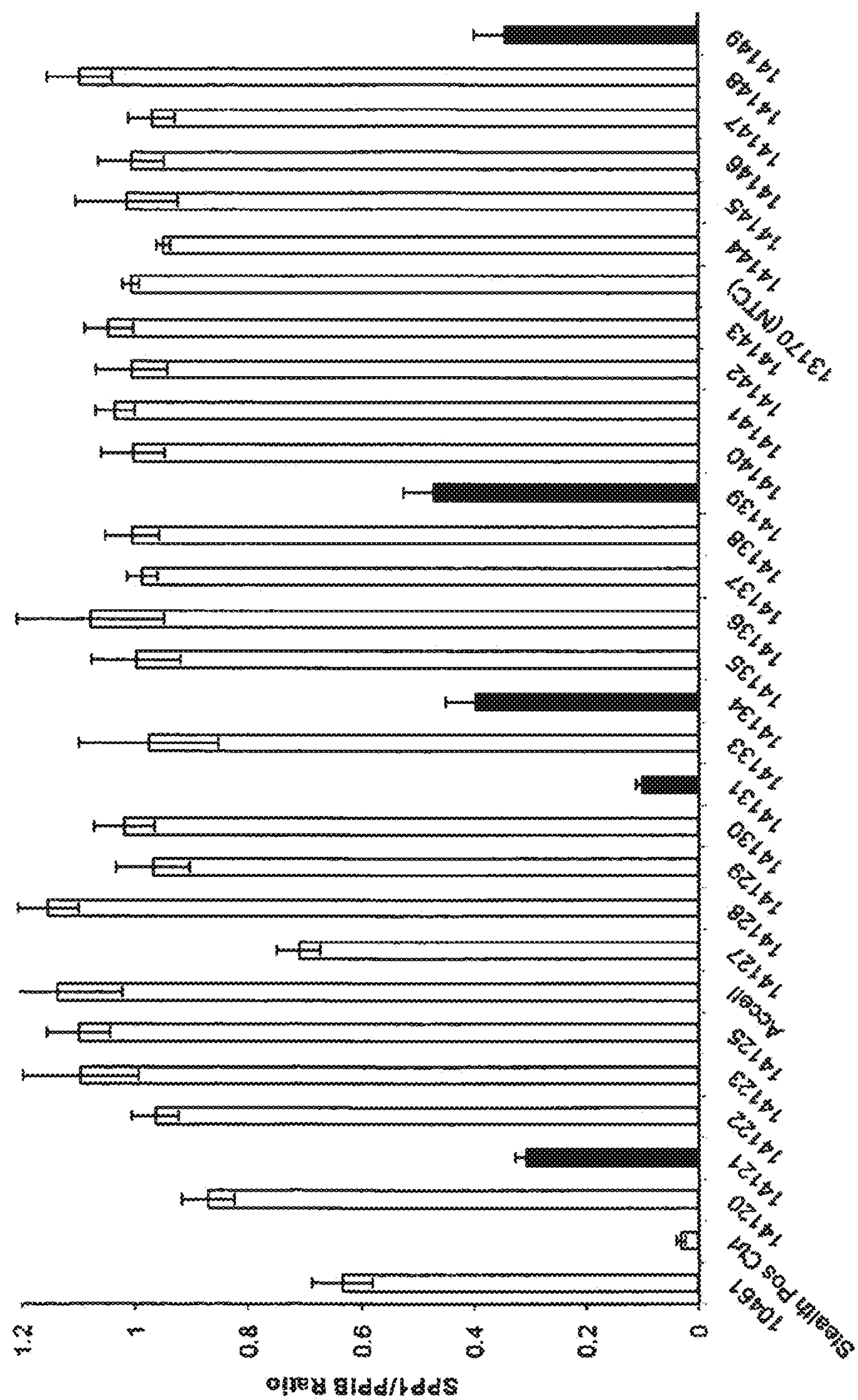
Local Delivery of *sd*-rxRNA™: Pilot Study



- 24 hours post delivery
- Hoechst and DY547

Figure 68

TARGET Screen Normalized T751 SPP1/PPIB Ratio
/bDNA/A-549 JL.032.1967 Cells rxRNA



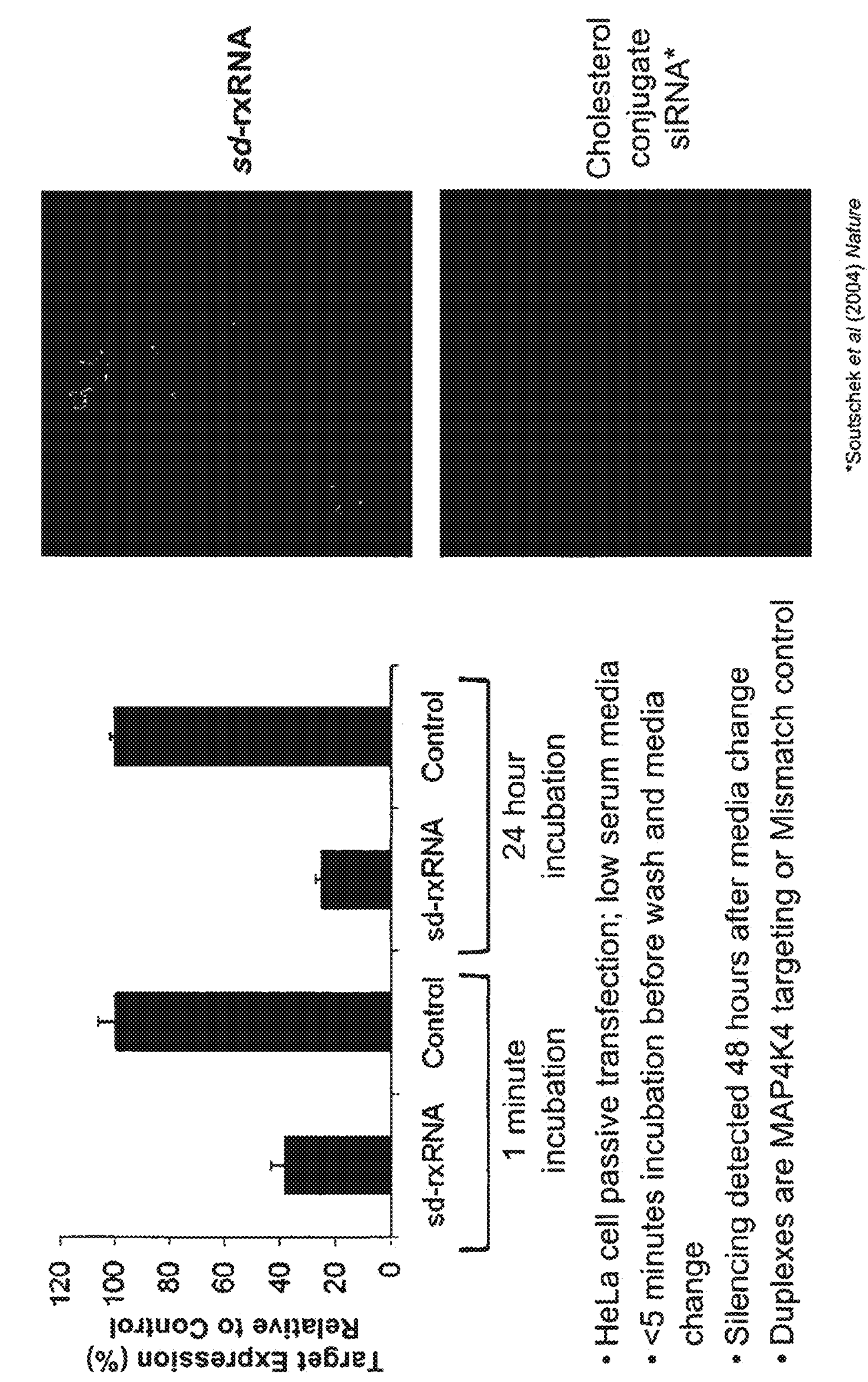

Target Expression (%) Relative to Control
120
100
80
60
40
20
0
sd-rxRNA
Control
sd-rxRNA
Control
1 minute incubation
24 hour incubation
• HeLa cell passive transfection; low serum media
• <5 minutes incubation before wash and media change
• Silencing detected 48 hours after media change
• Duplexes are MAP4K4 targeting or Mismatch control
sd-rxRNA
Cholesterol conjugate siRNA*
*Soutschek et al (2004) Nature

Figure 69

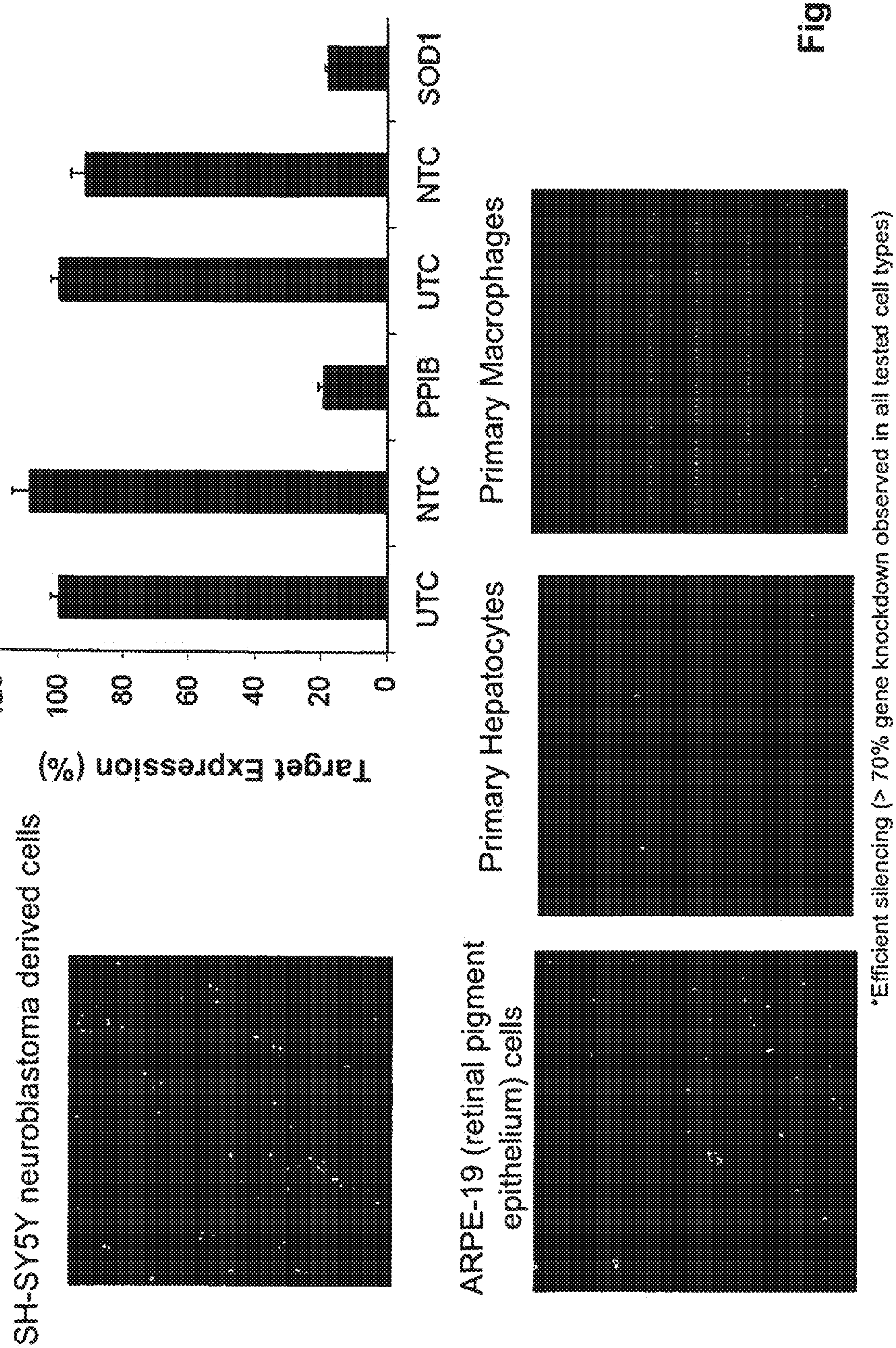

SH-SY5Y neuroblastoma derived cells
Target Expression (%)
120
100
80
60
40
20
0
UTC
NTC
PPIB
UTC
NTC
SOD1
Primary Hepatocytes
Primary Macrophages
ARPE-19 (retinal pigment epithelium) cells
*Efficient silencing (> 70% gene knockdown observed in all tested cell types)

Figure 70

Figure 71

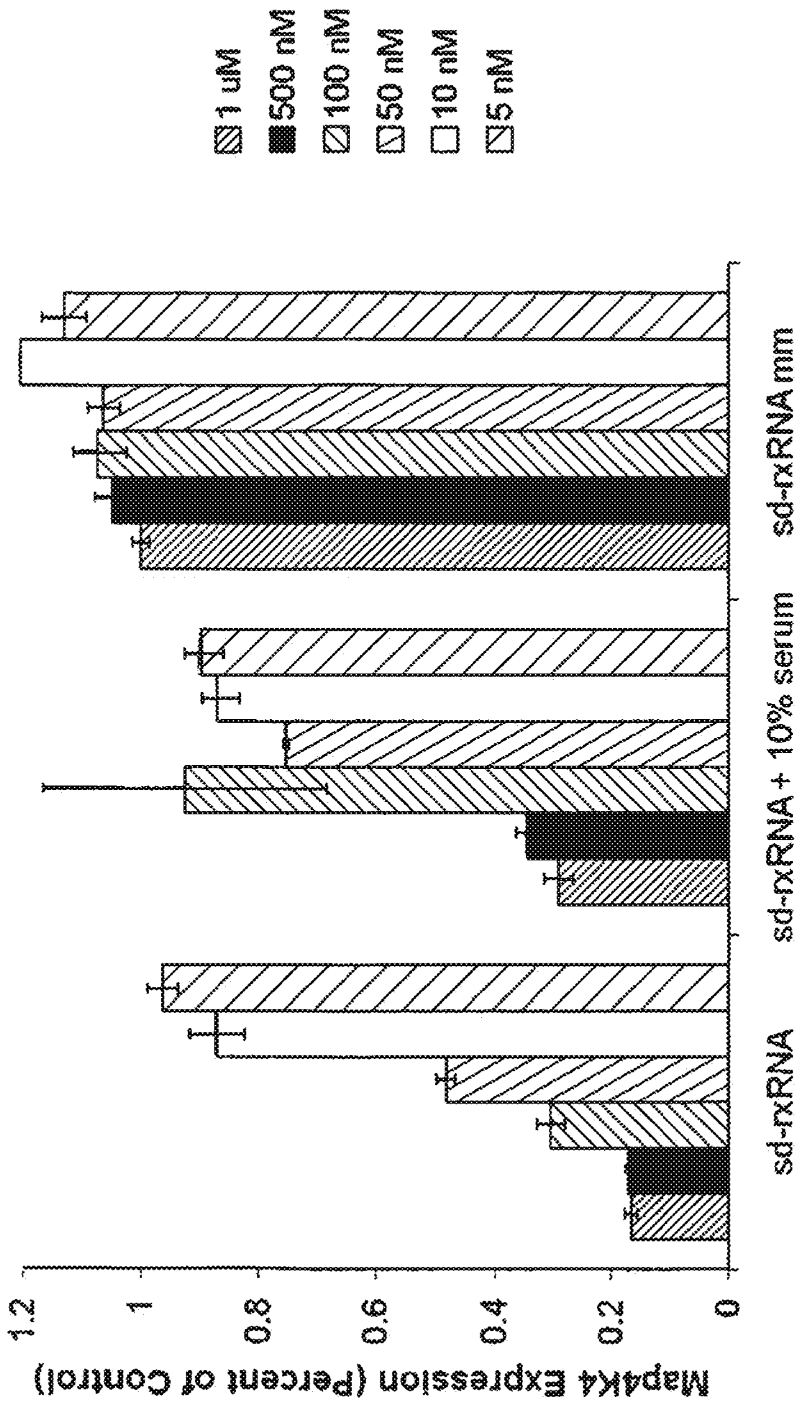
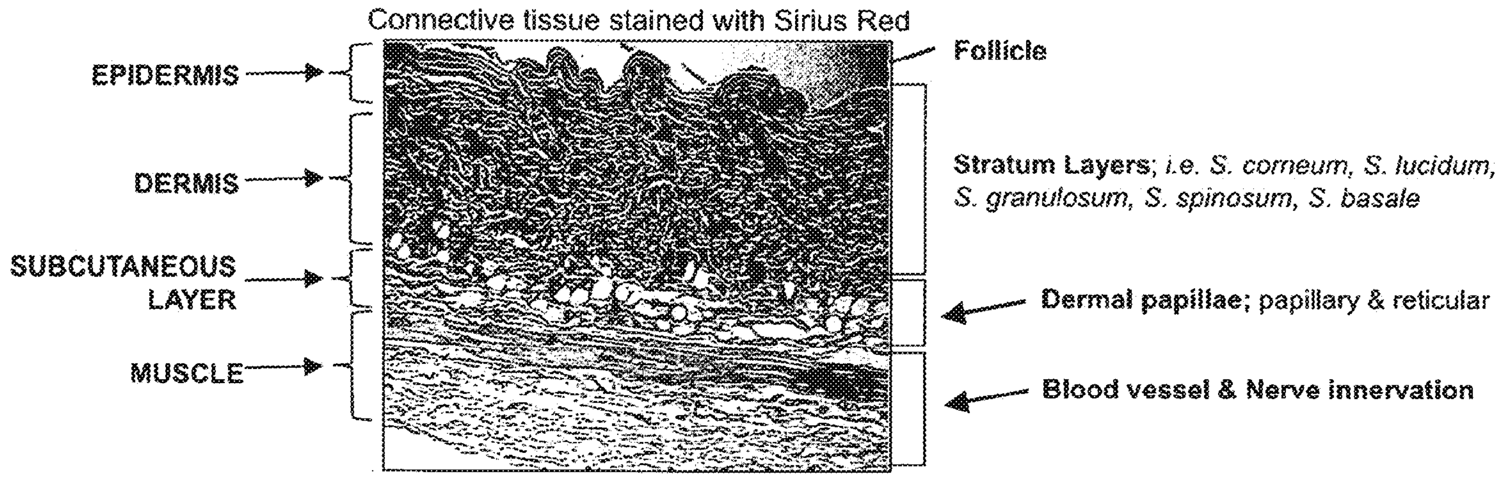
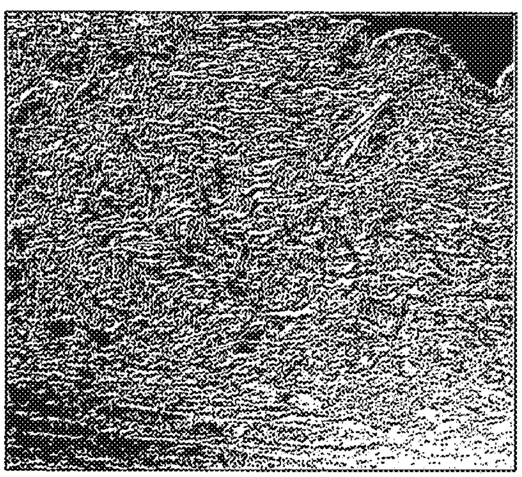
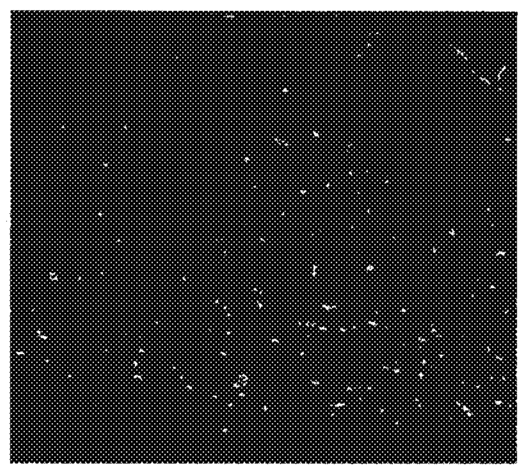

1 uM
500 nM
100 nM
50 nM
10 nM
5 nM
Map4K4 Expression (Percent of Control)
1.2
1
0.8
0.6
0.4
0.2
0
sd-rxRNA
sd-rxRNA + 10% serum
sd-rxRNA mm

Figure 72







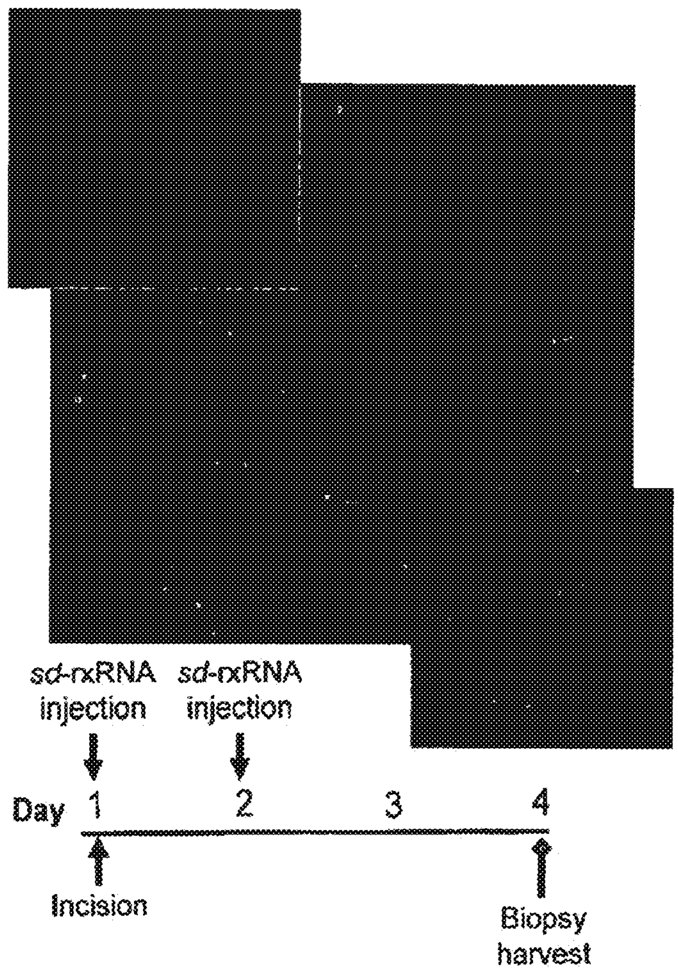
100 uL intradermal injection 1mM DY547-labeled *sd*-rxRNA (red)

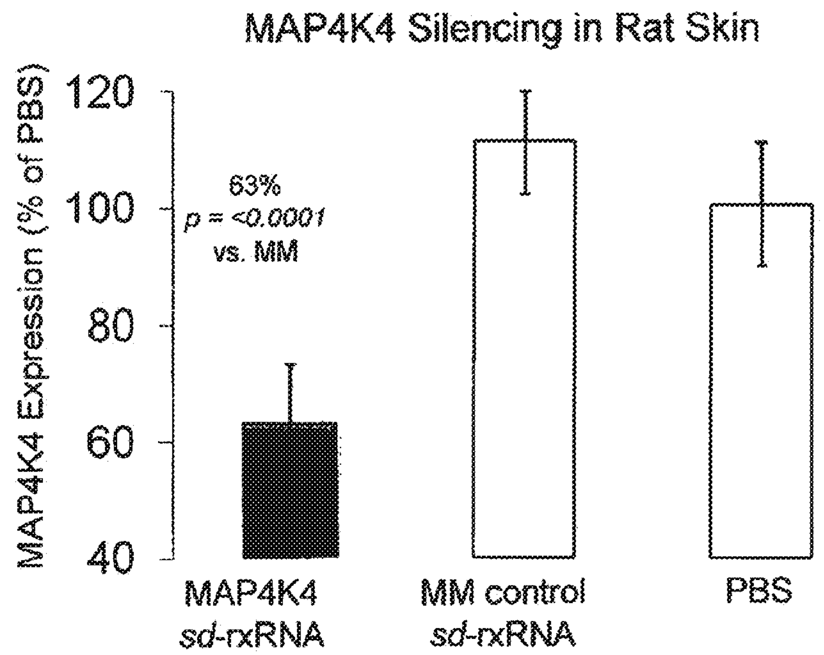
Biopsy harvested 4 days post injection

Sections were paraffin embedded, formalin fixed

Counterstained for nuclei (Hoechst - blue)

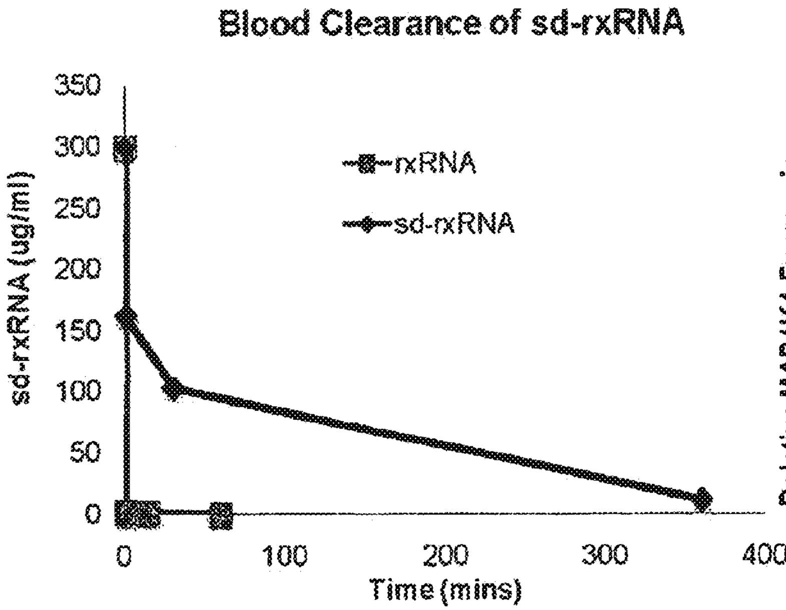
Figure 73



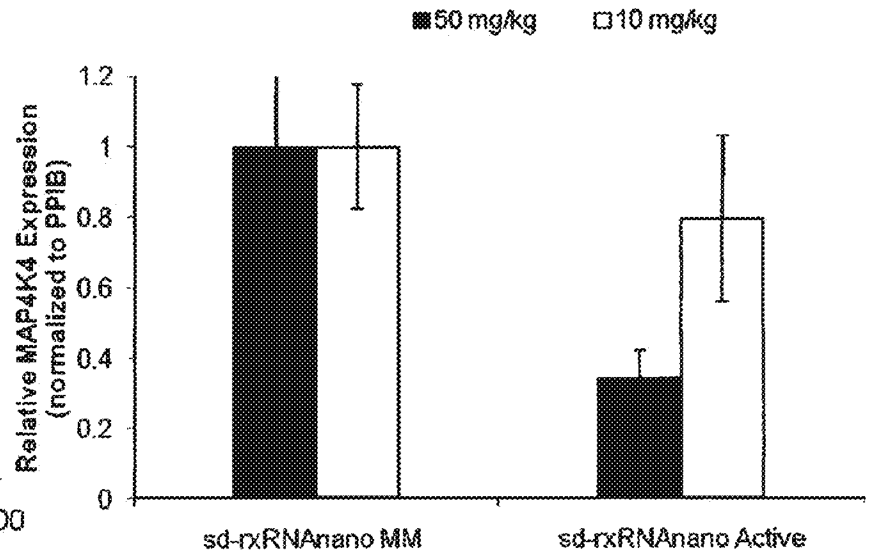


- n=8 injection sites, SD rats, 1 cm full face incisions, harvest 3 mm biopsies
- RNA prepared and target expression determined by QPCR
- Expression normalized to housekeeping gene cyclophilin B

Figure 74

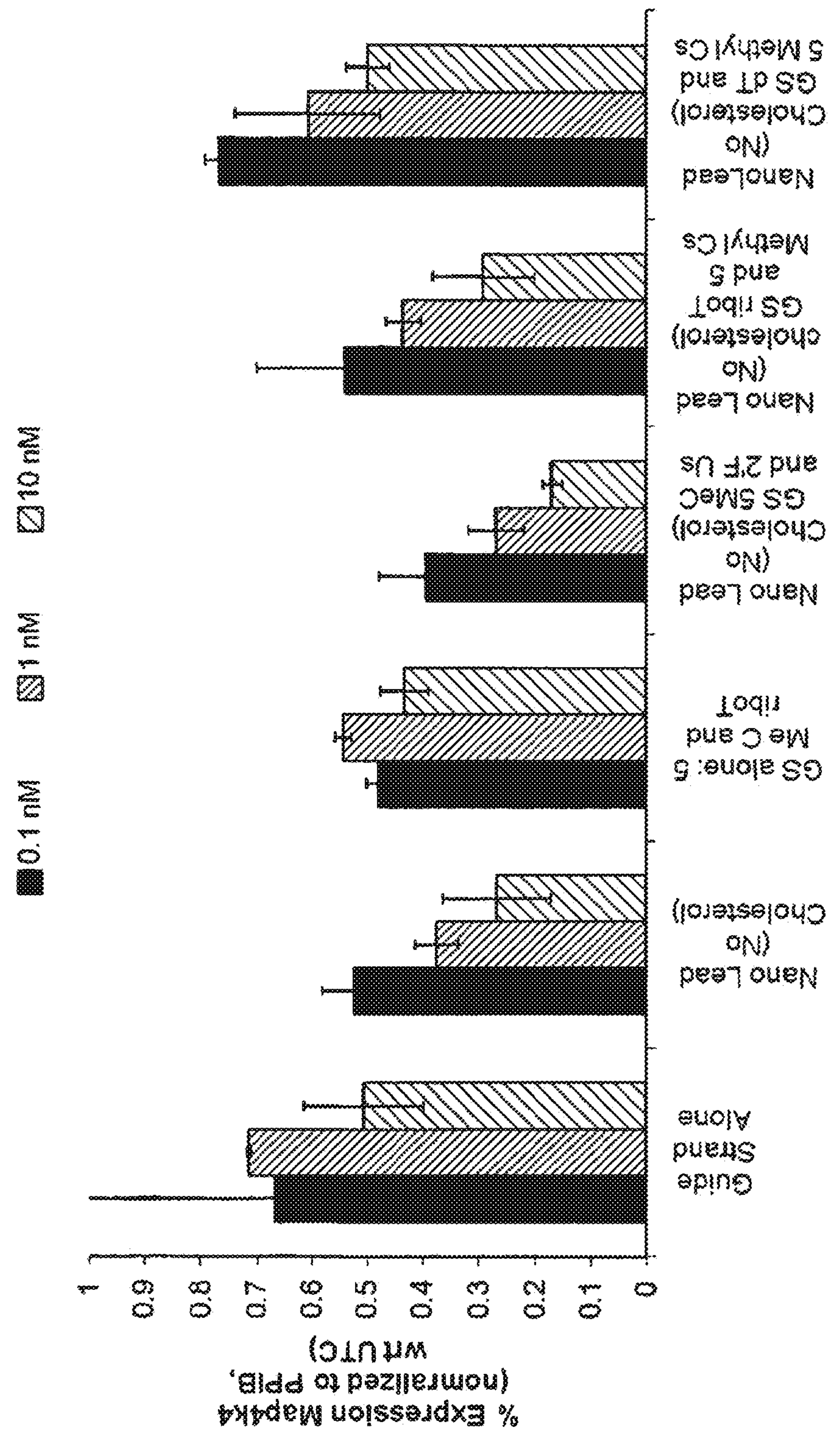


- Pilot Study: *sd*-rxRNA remaining in mouse blood (n=1)
- Detection of DY547-labeled RNA by fluorescence



- Visual fluorescence detection in tissue lysates (50 mg/kg dose)
- Confocal imaging confirms intracellular delivery
- Efficient silencing of targeted gene in liver as detected by RT-PCR

Figure 75


■ 0.1 nM
▨ 1 nM
▨ 10 nM
% Expression Map4k4 (nomralized to PPIB, wrt UTC)
0
0.1
0.2
0.3
0.4
0.5
0.6
0.7
0.8
0.9
1
Guide Strand Alone
Nano Lead (No Cholesterol)
GS alone: 5 Me C and riboT
Nano Lead (No Cholesterol) GS 5MeC and 2'F Us
Nano Lead (No cholesterol) GS riboT and 5 Methyl Cs
NanoLead (No Cholesterol) GS dT and 5 Methyl Cs

Incorporation of 5 Me C and/or ribothymidine in Guide Strand Reduces Efficacy

Passive Uptake

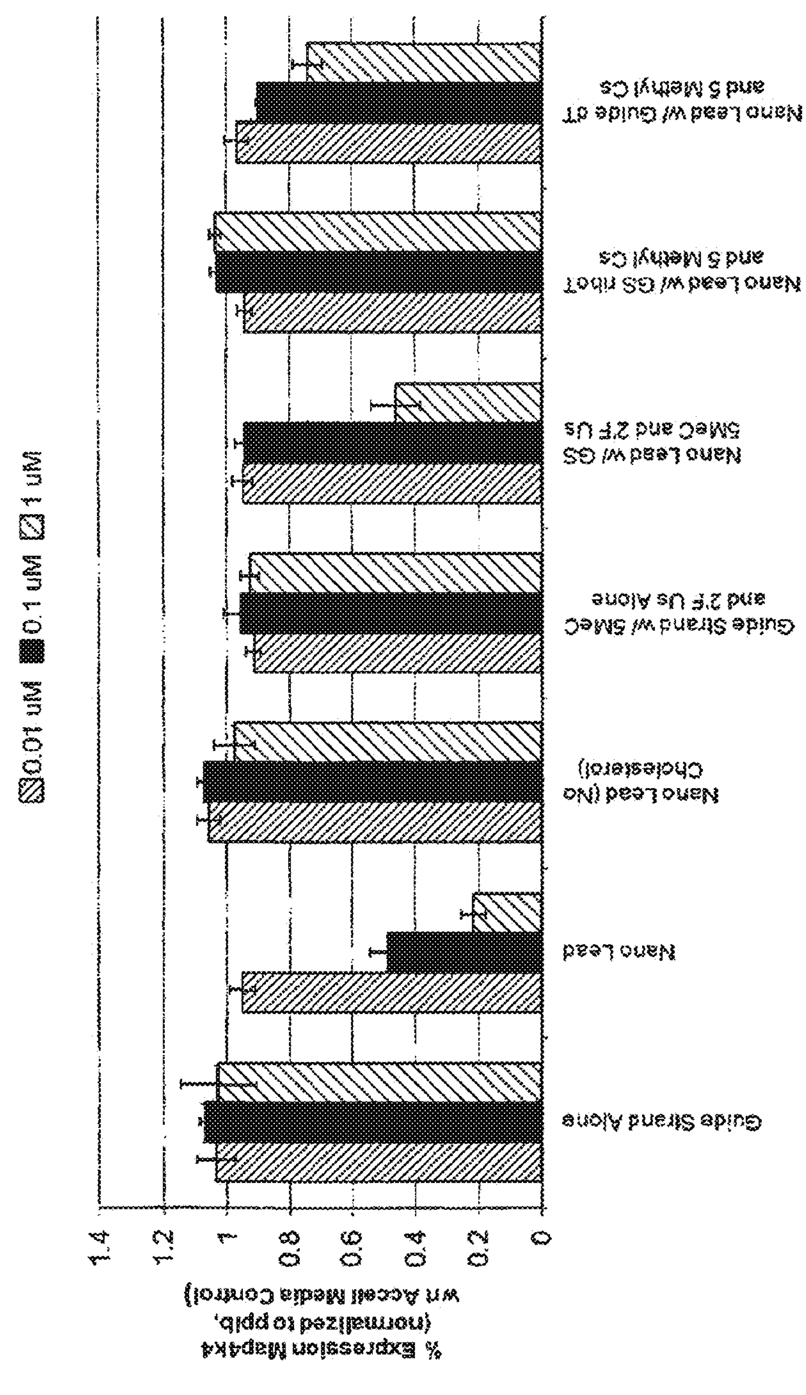
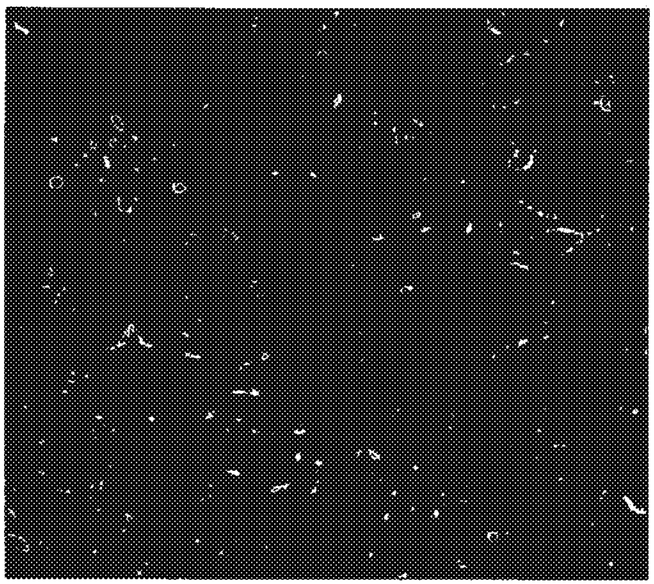


Figure 76

Figure 77

sd-rxRNA^{nano} *vs.* Competitor: Systemic Delivery to the Liver

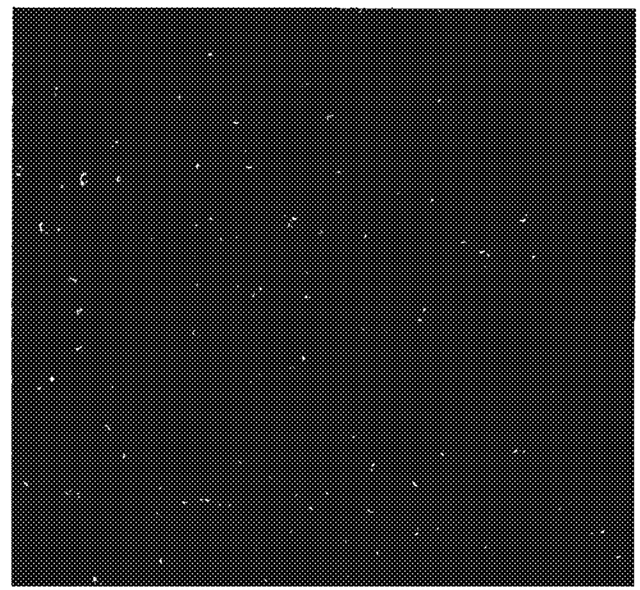
sd-rxRNA^{nano}



gain = 380; 50 mg/kg

Competitor conjugate*

*Soutschek et al (2004) *Nature* , 432:173



gain ≈400; 50 mg/kg

Figure 78

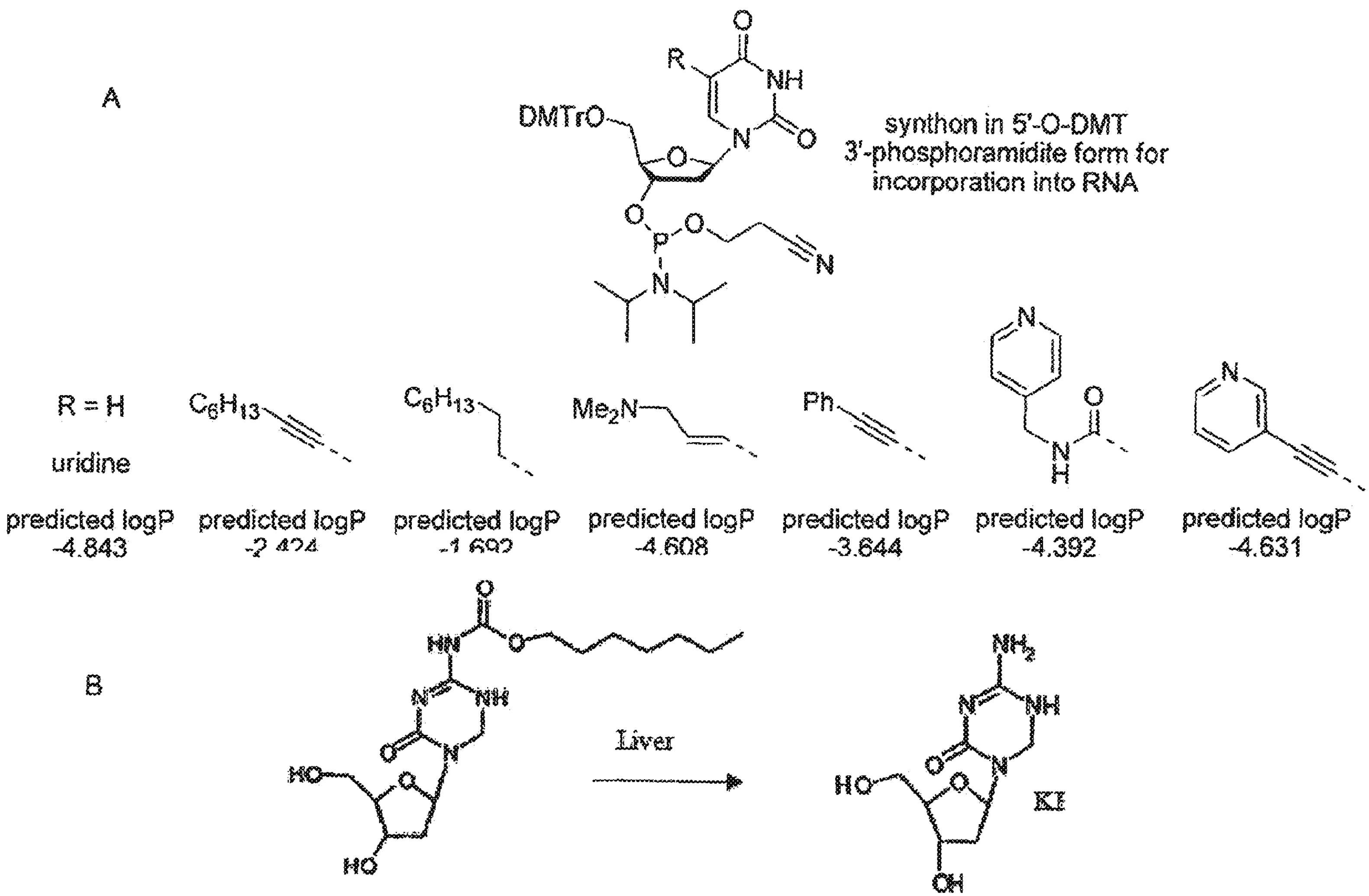
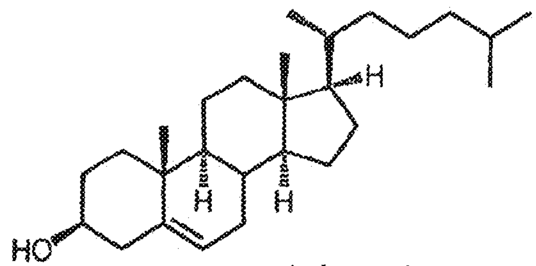
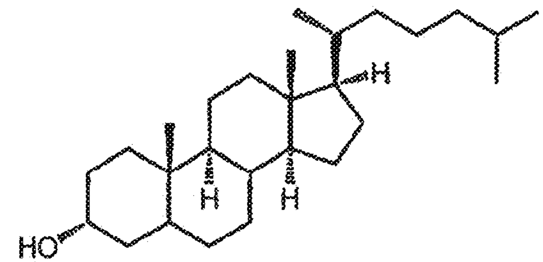

A
R
NH
O
DMTrO
N
O
P
N
synthon in 5'-O-DMT
3'-phosphoramidite form for
incorporation into RNA
R = H
uridine
predicted logP
-4.843
C_6H_{13}
predicted logP
-2.424
C_6H_{13}
predicted logP
-1.692
Me_2N
predicted logP
-4.608
Ph
predicted logP
-3.644
N
O
N
H
predicted logP
-4.392
N
predicted logP
-4.631
B
HN
NH
HO
Liver
NH_2
NH
HO
OH
KI

Figure 79



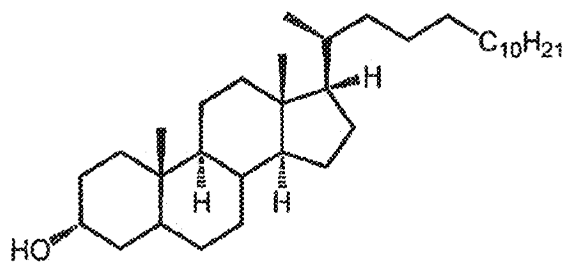
cholesterol

predicted logP = 7.132



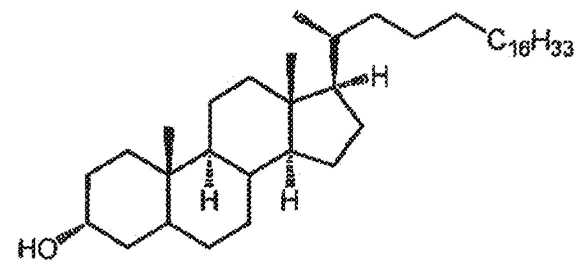
cholesterol analog derived from lithocholic acid with isopropyl bromide Grignard reaction

predicted logP = 7.316



long side chain cholesterol analog derived from lithocholic acid with decyl bromide Grignard reaction

predicted logP = 9.433



very long side chain cholesterol analog derived from lithocholic acid with cetyl bromide Grignard reaction

predicted logP = 9.977

Figure 80

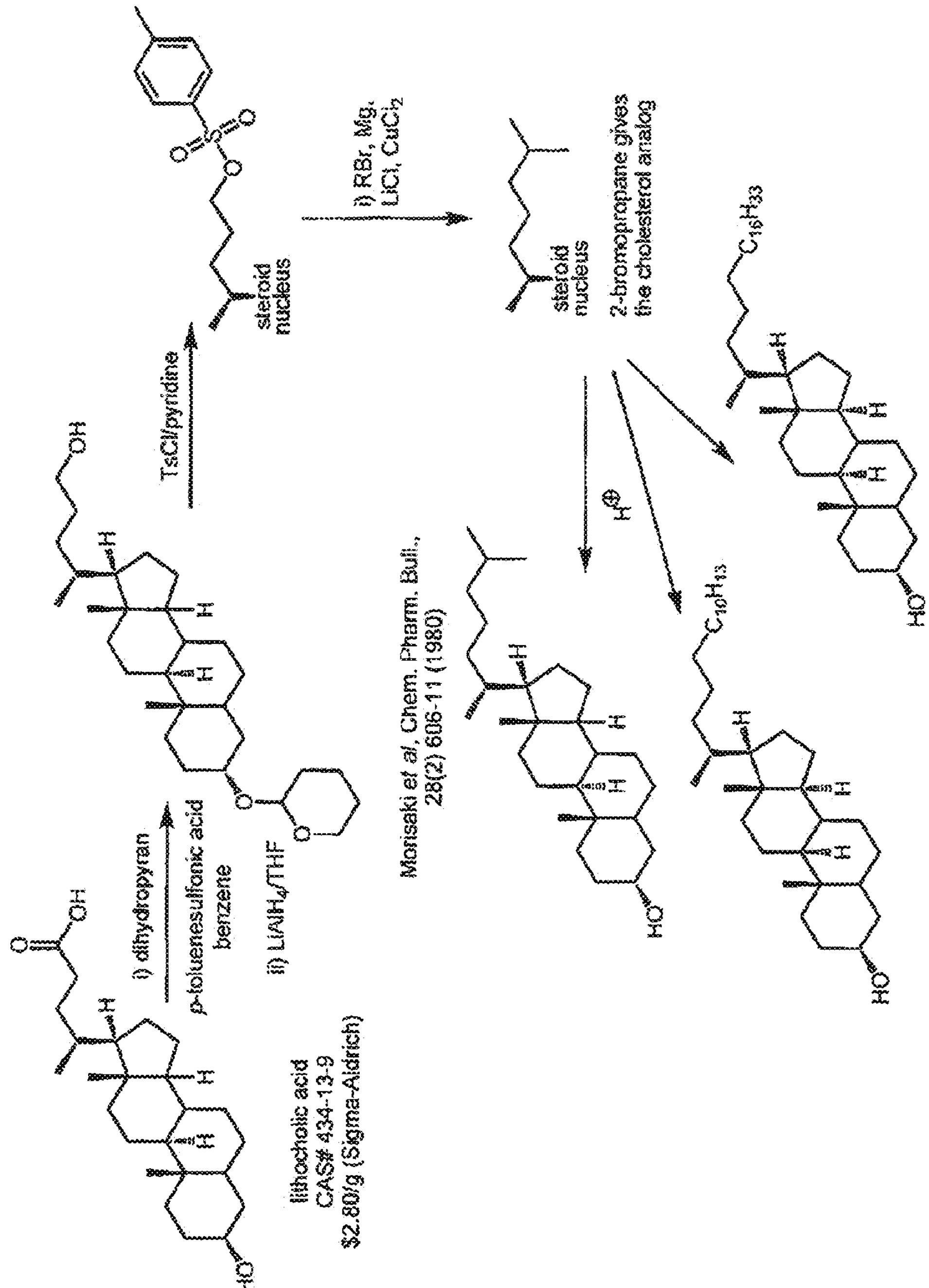

lithocholic acid
CAS# 434-13-9
$2.80/g (Sigma-Aldrich)
i) dihydropyran
p-toluenesulfonic acid
benzene
ii) LiAlH4/THF
TsCl/pyridine
steroid nucleus
i) RBr, Mg,
LiCl, CuCl2
steroid nucleus
2-bromopropane gives
the cholesterol analog
Morisaki et al, Chem. Pharm. Bull.,
28(2) 606-11 (1980)
C10H13
C15H33

Figure 81

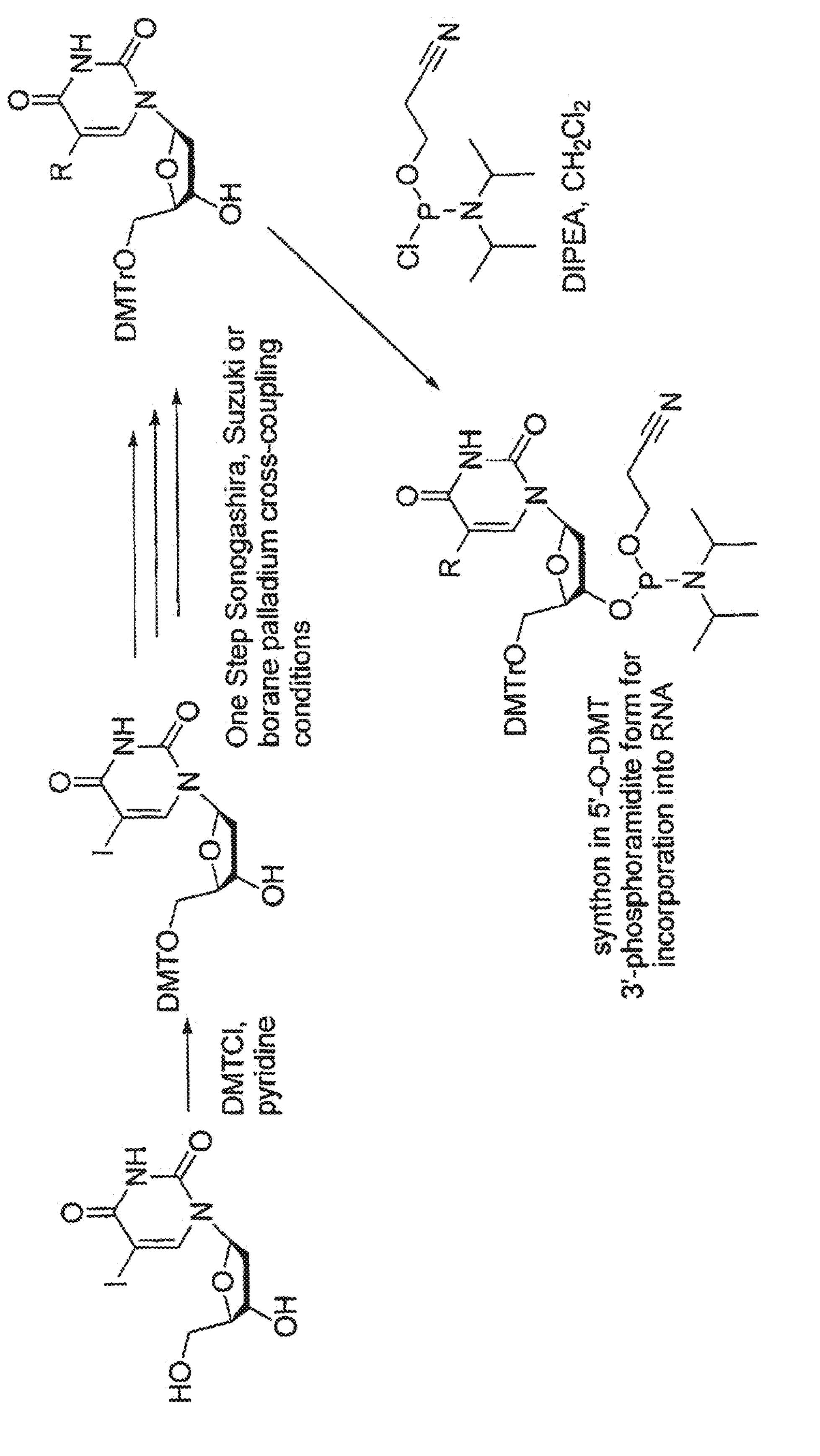

DMTCl,
pyridine
One Step Sonogashira, Suzuki or
borane palladium cross-coupling
conditions
DIPEA, CH_2Cl_2
synthon in 5'-O-DMT
3'-phosphoramidite form for
incorporation into RNA

Figure 82

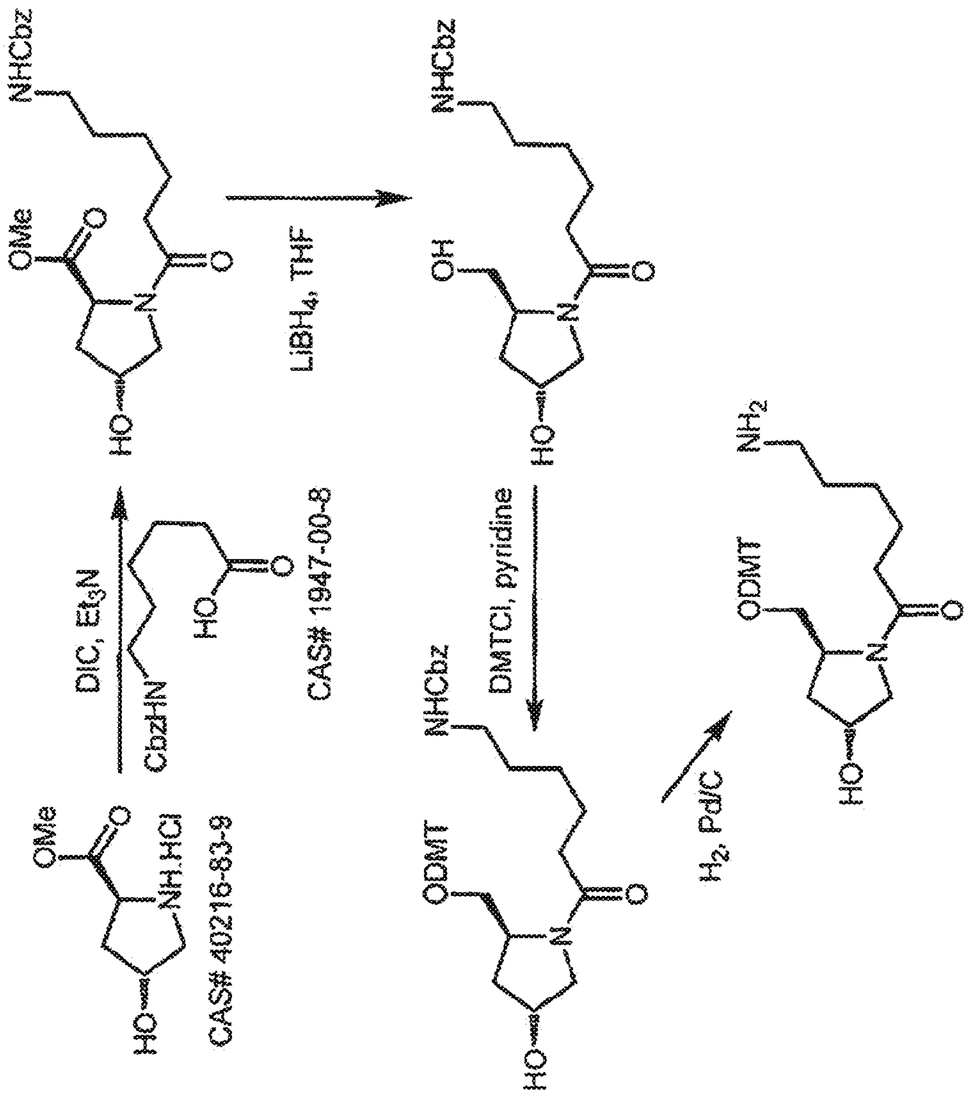

OMe
NH.HCl
HO
CAS# 40216-83-9
DIC, Et$_3$N
CbzHN
HO
O
CAS# 1947-00-8
NHCbz
LiBH$_4$, THF
OH
DMTCl, pyridine
ODMT
H$_2$, Pd/C
NH$_2$

Figure 83

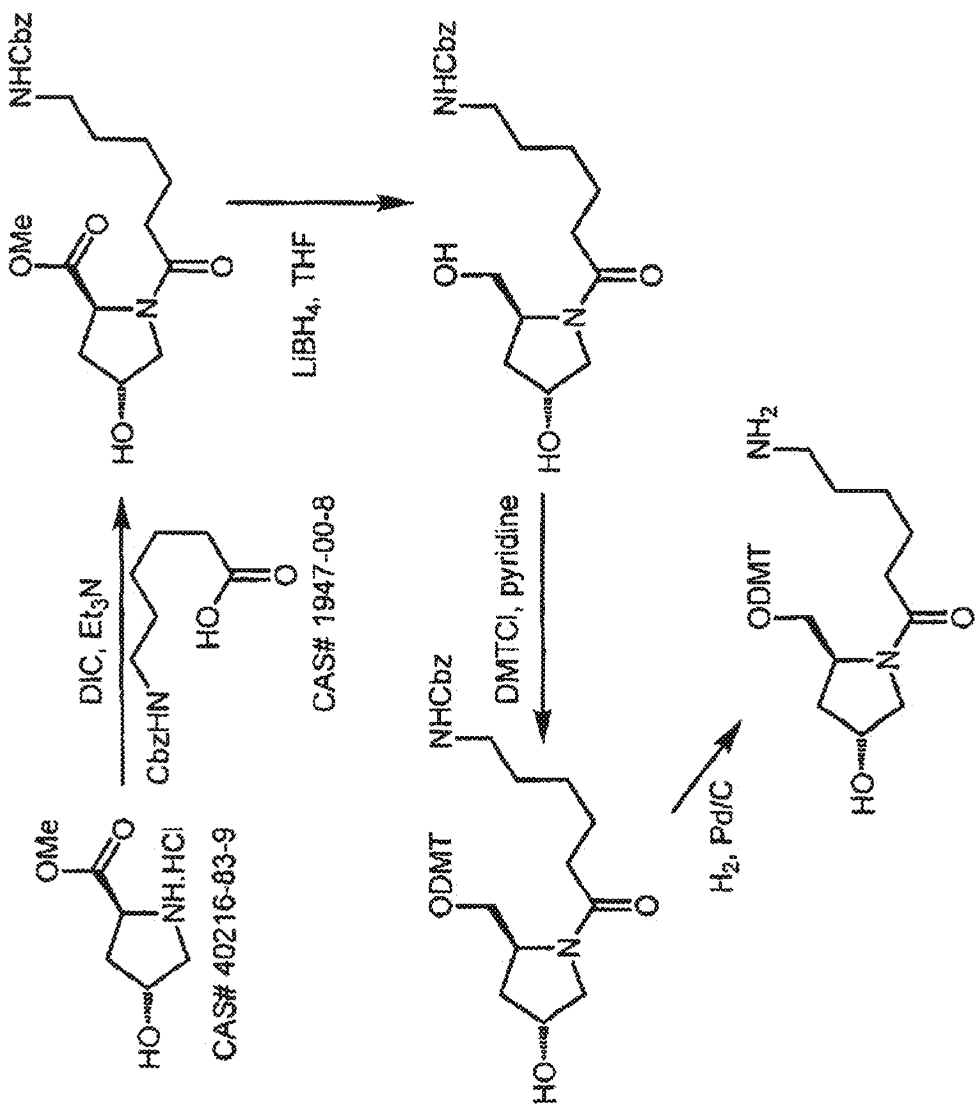

OMe
NH.HCl
HO
CAS# 40216-83-9
DIC, Et_3N
CbzHN
HO
CAS# 1947-00-8
NHCbz
N
$LiBH_4$, THF
OH
DMTCl, pyridine
ODMT
H_2, Pd/C
NH_2

Figure 84

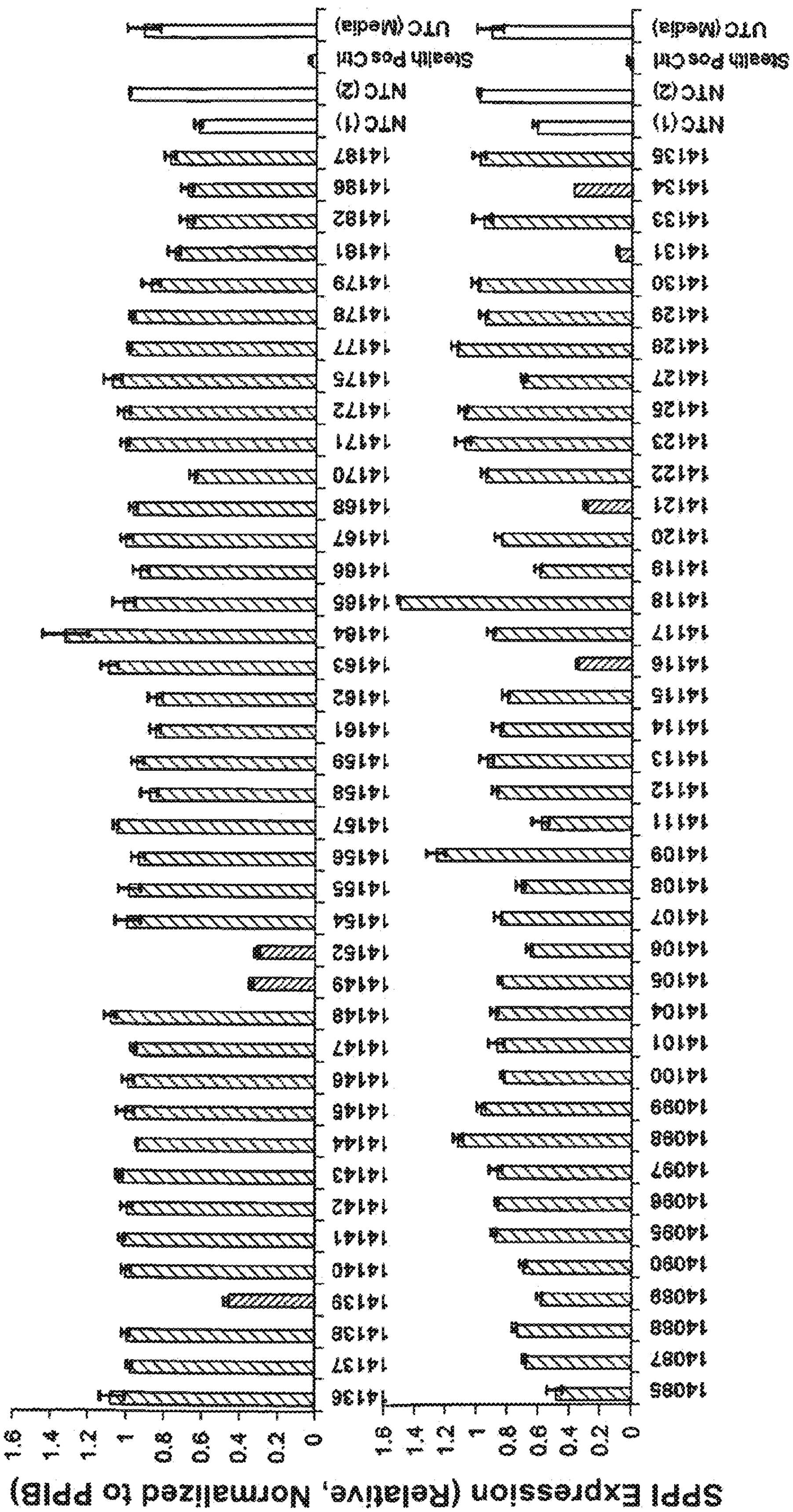

SPPI Expression (Relative, Normalized to PPIB)
1.6
1.4
1.2
1
0.8
0.6
0.4
0.2
0
14136
14137
14138
14139
14140
14141
14142
14143
14144
14145
14146
14147
14148
14149
14152
14154
14155
14156
14157
14158
14159
14161
14162
14163
14164
14165
14166
14167
14168
14170
14171
14172
14175
14177
14178
14179
14181
14182
14186
14187
NTC (1)
NTC (2)
Stealth Pos Ctrl
UTC (Media)
14085
14087
14088
14089
14090
14095
14096
14097
14098
14099
14100
14101
14104
14105
14106
14107
14108
14109
14111
14112
14113
14114
14115
14116
14117
14118
14119
14120
14121
14122
14123
14126
14127
14128
14129
14130
14131
14133
14134
14135

Figure 85

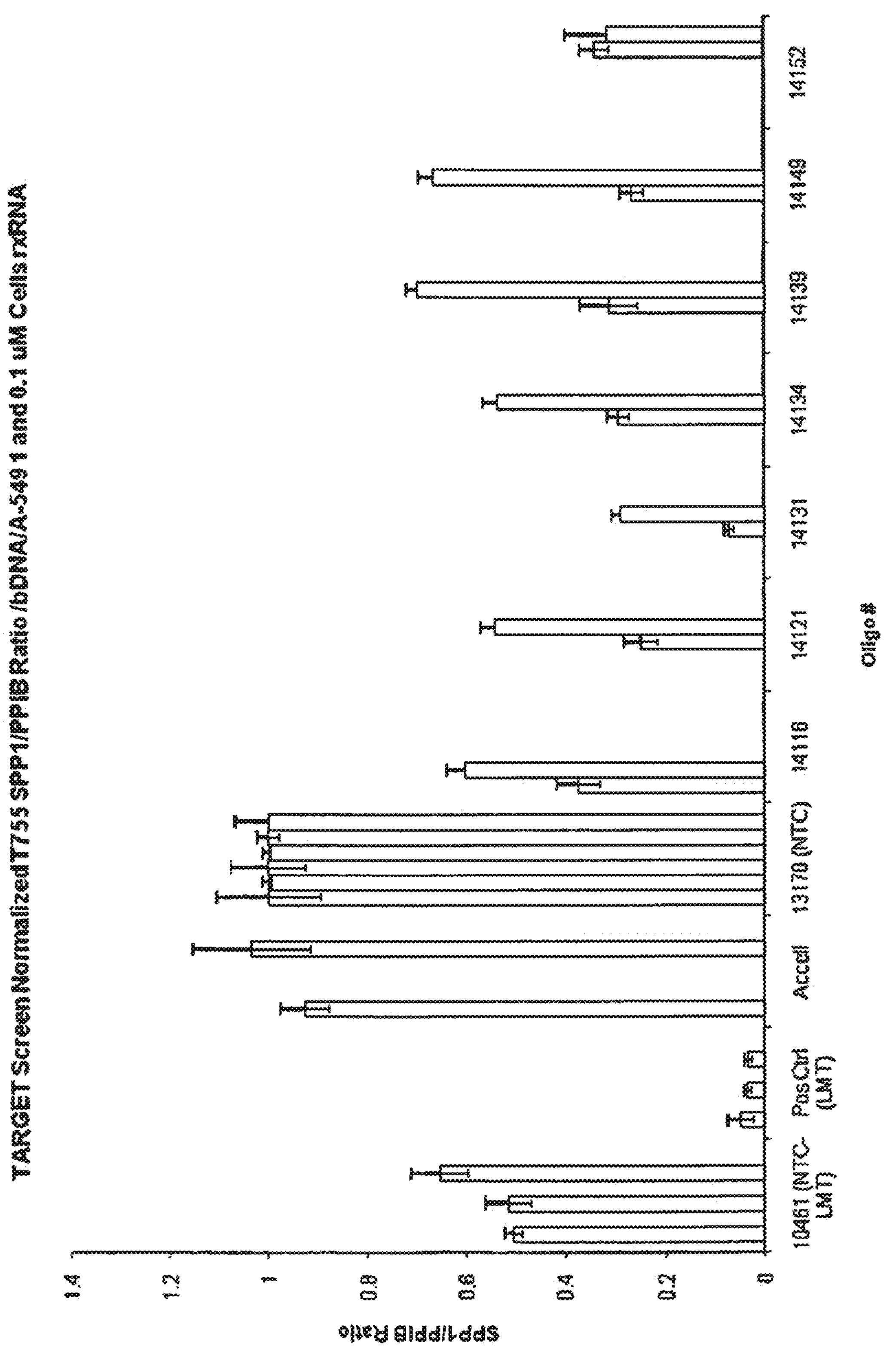
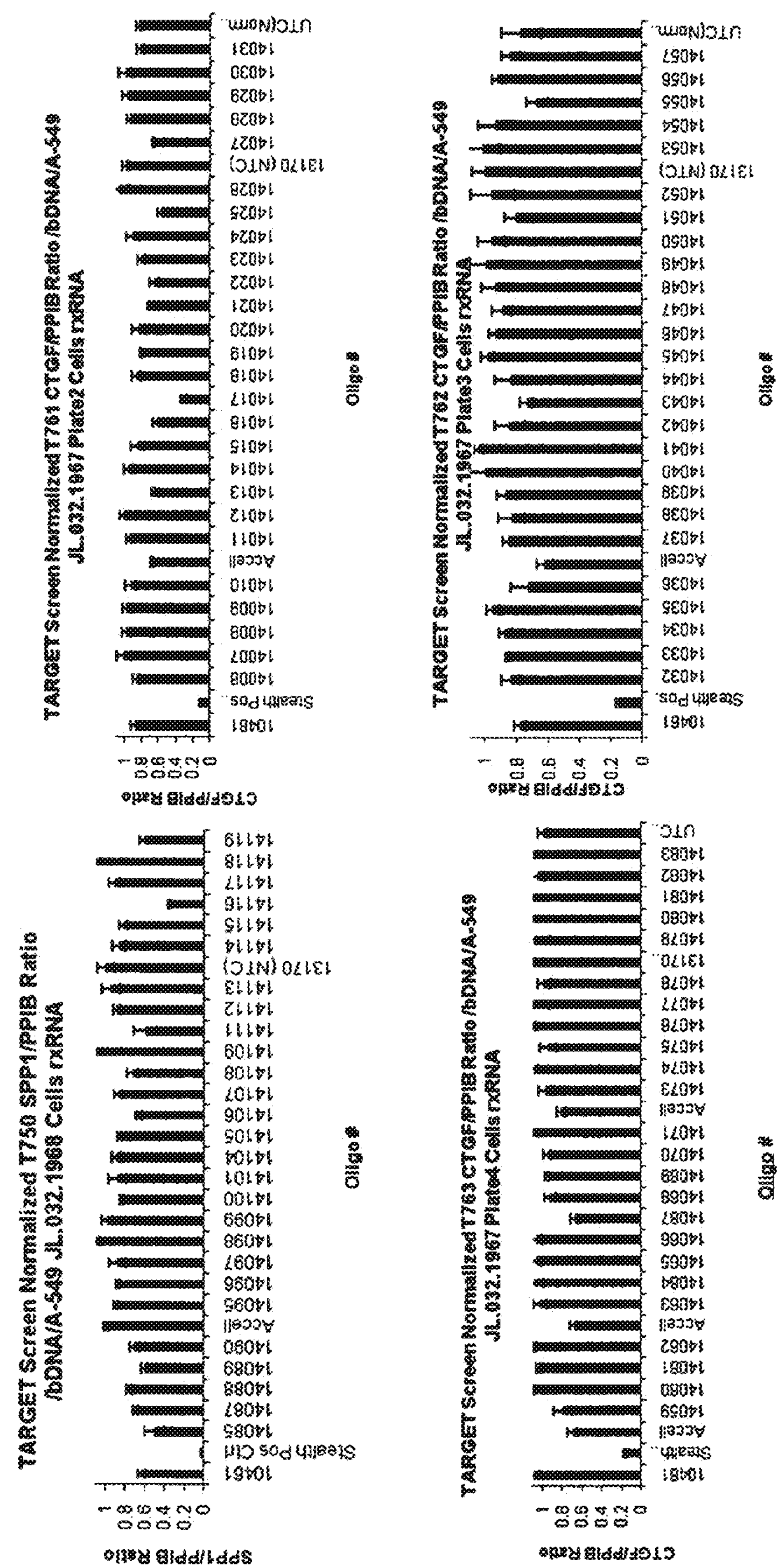

TARGET Screen Normalized T755 SPP1/PPIB Ratio /bDNA/A-549 1 and 0.1 uM Cells mRNA
SPP-1/PPIB Ratio
0
0.2
0.4
0.6
0.8
1
1.2
1.4
10461 (NTC-LMT)
PosCtrl (LMT)
Accell
13170 (NTC)
14116
14121
14131
14134
14139
14149
14152
Oligo #

Figure 86


TARGET Screen Normalized T761 CTGF/PPIB Ratio /bDNA/A-549
JL.032.1967 Plate2 Cells rxRNA
CTGF/PPIB Ratio
Oligo #
TARGET Screen Normalized T762 CTGF/PPIB Ratio /bDNA/A-549
JL.032.1967 Plate3 Cells rxRNA
CTGF/PPIB Ratio
Oligo #
TARGET Screen Normalized T750 SPP1/PPIB Ratio
/bDNA/A-549 JL.032.1968 Cells rxRNA
SPP1/PPIB Ratio
Oligo #
TARGET Screen Normalized T763 CTGF/PPIB Ratio /bDNA/A-549
JL.032.1967 Plate4 Cells rxRNA
CTGF/PPIB Ratio
Oligo #

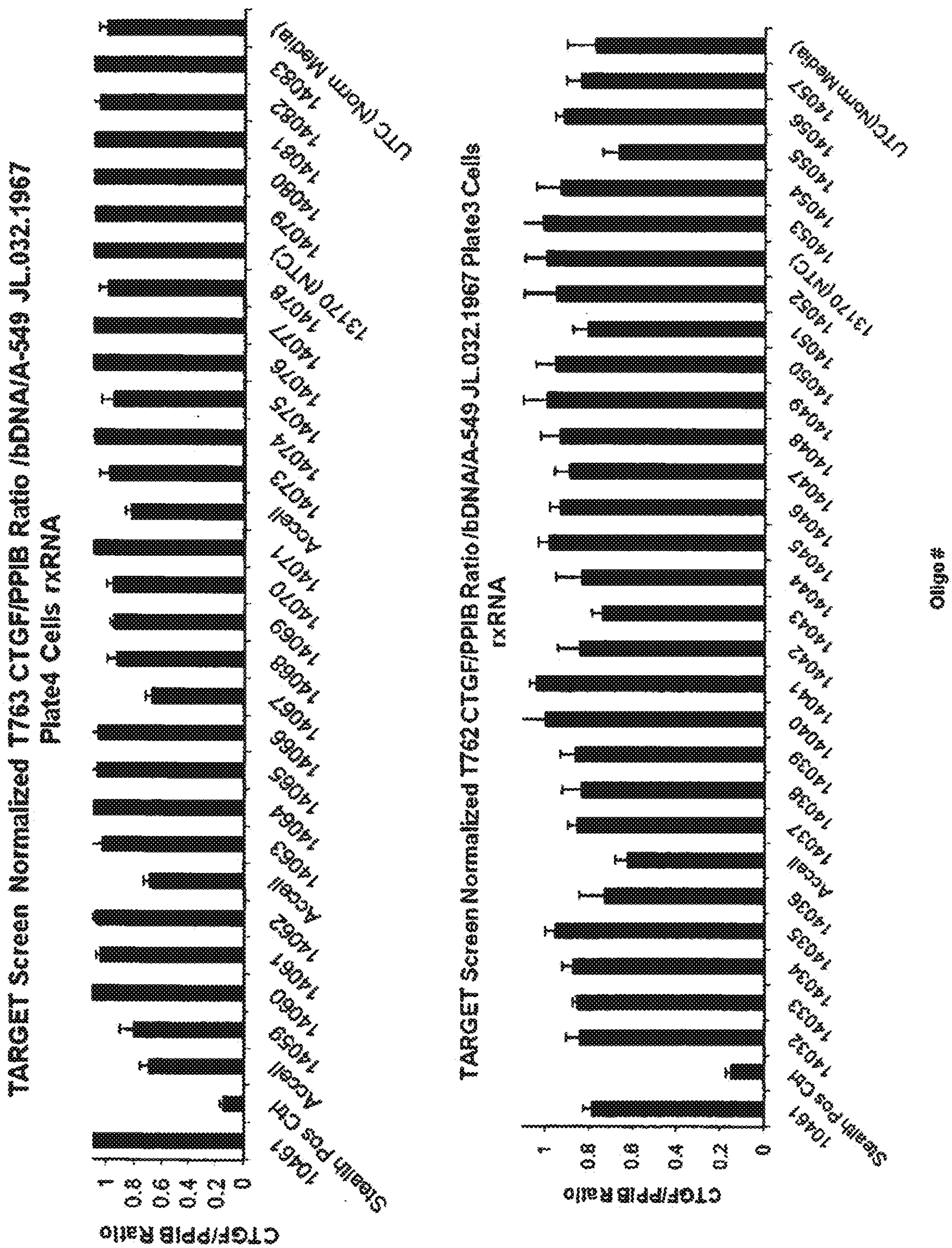

TARGET Screen Normalized T763 CTGF/PPIB Ratio /bDNA/A-549 JL.032.1967 Plate4 Cells rxRNA
CTGF/PPIB Ratio
TARGET Screen Normalized T762 CTGF/PPIB Ratio /bDNA/A-549 JL.032.1967 Plate3 Cells rxRNA
CTGF/PPIB Ratio
Oligo #

Figure 87

Figure 88

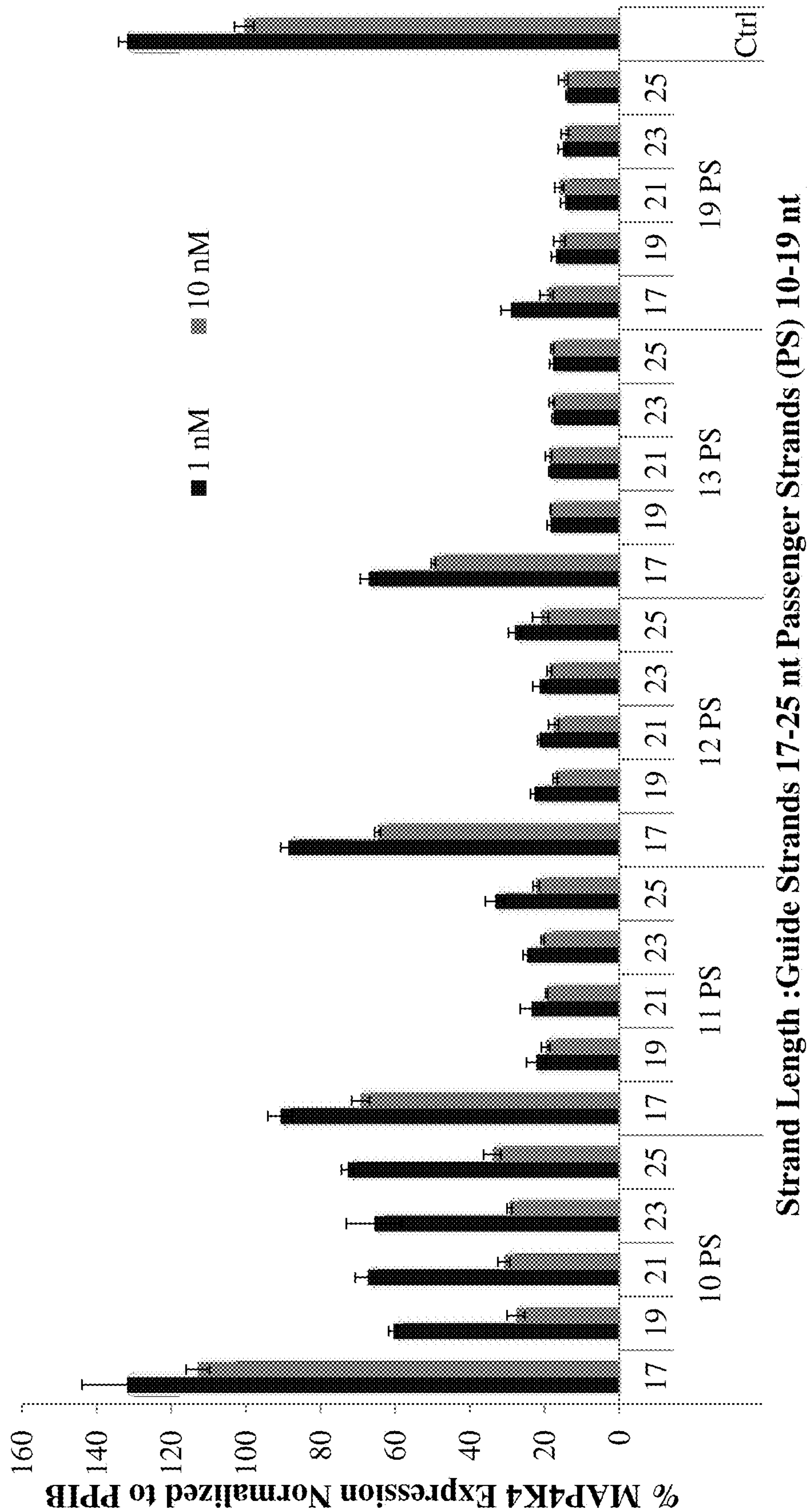
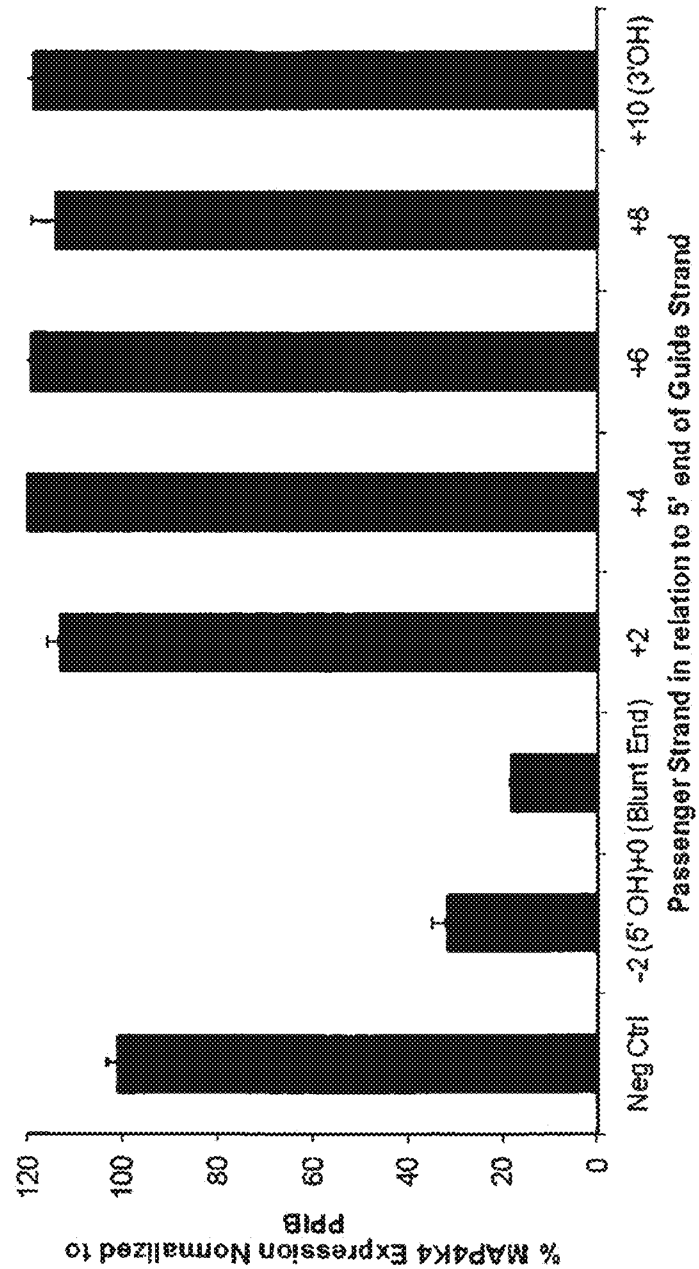

■ 1 nM
▩ 10 nM
% MAP4K4 Expression Normalized to PPIB
0
20
40
60
80
100
120
140
160
17
19
21
23
25
10 PS
11 PS
12 PS
13 PS
19 PS
Ctrl
Strand Length :Guide Strands 17-25 nt Passenger Strands (PS) 10-19 nt

Figure 89



% MAP4K4 Expression Normalized to PPIB
0
20
40
60
80
100
120
Neg Ctrl
-2 (5' OH)
+0 (Blunt End)
+2
+4
+6
+8
+10 (3'OH)
Passenger Strand in relation to 5' end of Guide Strand

Figure 90

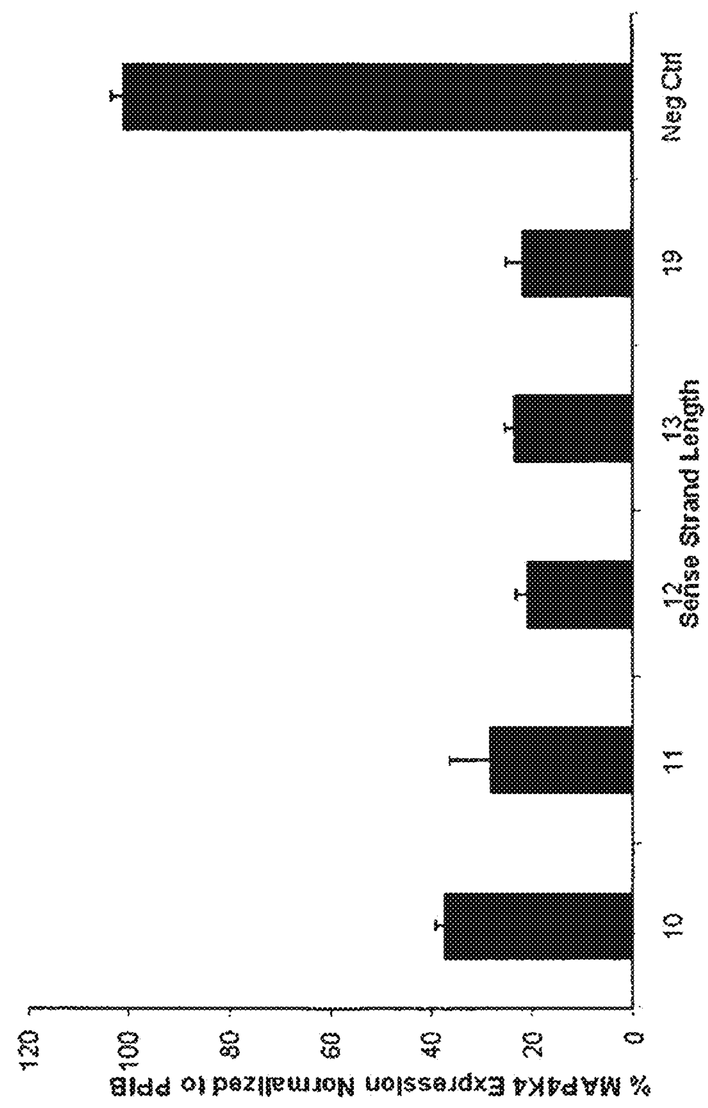

% MAP4K4 Expression Normalized to PPIB
120
100
80
60
40
20
0
10
11
12
13
19
Neg Ctrl
Sense Strand Length

Figure 91

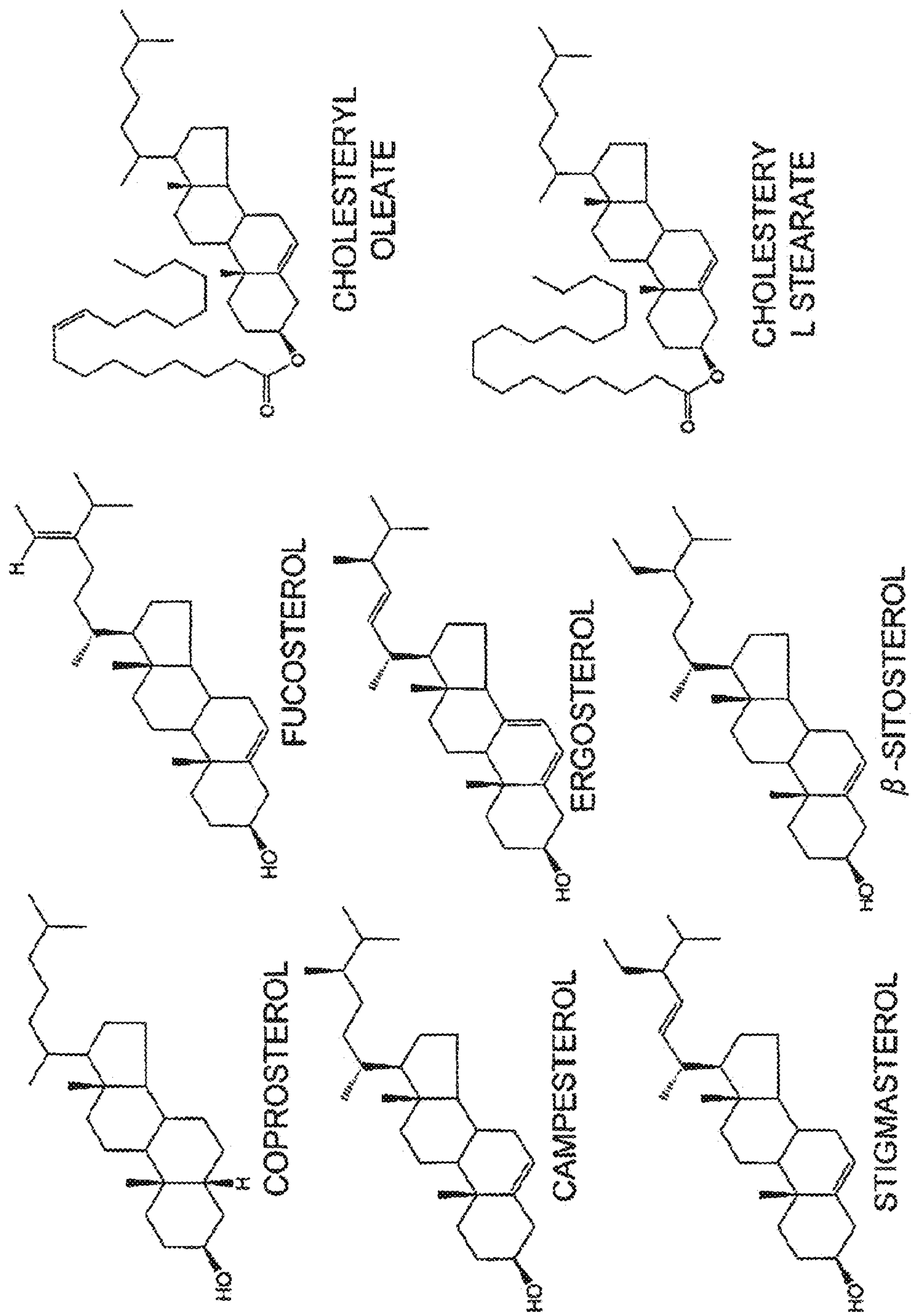
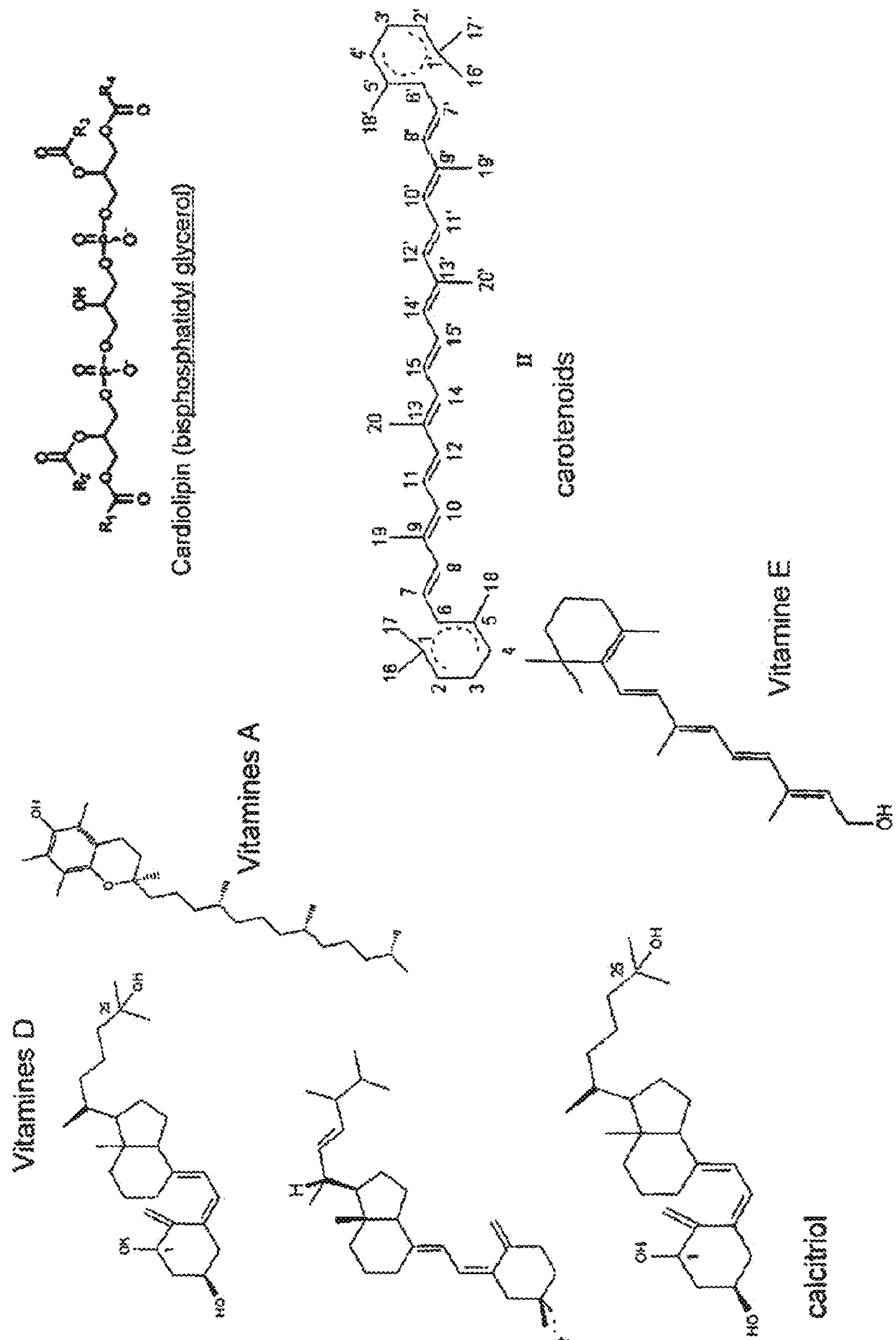

CHOLESTERYL OLEATE
CHOLESTERY L STEARATE
FUCOSTEROL
ERGOSTEROL
β-SITOSTEROL
COPROSTEROL
CAMPESTEROL
STIGMASTEROL

Figure 92


Cardiolipin (bisphosphatidyl glycerol)
carotenoids
Vitamines A
Vitamine E
Vitamines D
calcitriol

REDUCED SIZE SELF-DELIVERING RNAI COMPOUNDS

RELATED APPLICATIONS

This application claims the benefit under 35 U.S.C. §119(e) of U.S. provisional application serial number U.S. 61/192,954, entitled "Chemically Modified Polynucleotides and Methods of Using the Same," filed on Sep. 22, 2008, U.S. 61/149,946, entitled "Minimum Length Triggers of RNA Interference," filed on Feb. 4, 2009, and U.S. 61/224,031, entitled "Minimum Length Triggers of RNA Interference," filed on Jul. 8, 2009, the disclosure of each of which is incorporated by reference herein in its entirety.

FIELD OF INVENTION

The invention pertains to the field of RNA interference (RNAi). The invention more specifically relates to nucleic acid molecules with improved in vivo delivery properties without the use of a delivering agent and their use in efficient gene silencing.

BACKGROUND OF INVENTION

Complementary oligonucleotide sequences are promising therapeutic agents and useful research tools in elucidating gene functions. However, prior art oligonucleotide molecules suffer from several problems that may impede their clinical development, and frequently make it difficult to achieve intended efficient inhibition of gene expression (including protein synthesis) using such compositions in vivo.

A major problem has been the delivery of these compounds to cells and tissues. Conventional double-stranded RNAi compounds, 19-29 bases long, form a highly negatively-charged rigid helix of approximately 1.5 by 10-15 nm in size. This rod type molecule cannot get through the cell-membrane and as a result has very limited efficacy both in vitro and in vivo. As a result, all conventional RNAi compounds require some kind of a delivery vehicle to promote their tissue distribution and cellular uptake. This is considered to be a major limitation of the RNAi technology.

There have been previous attempts to apply chemical modifications to oligonucleotides to improve their cellular uptake properties. One such modification was the attachment of a cholesterol molecule to the oligonucleotide. A first report on this approach was by Letsinger et al., in 1989. Subsequently, ISIS Pharmaceuticals, Inc. (Carlsbad, Calif.) reported on more advanced techniques in attaching the cholesterol molecule to the oligonucleotide (Manoharan, 1992).

With the discovery of siRNAs in the late nineties, similar types of modifications were attempted on these molecules to enhance their delivery profiles. Cholesterol molecules conjugated to slightly modified (Soutschek, 2004) and heavily modified (Wolfrum, 2007) siRNAs appeared in the literature. Yamada et al., 2008 also reported on the use of advanced linker chemistries which further improved cholesterol mediated uptake of siRNAs. In spite of all this effort, the uptake of these types of compounds appears to be inhibited in the presence of biological fluids resulting in highly limited efficacy in gene silencing in vivo, limiting the applicability of these compounds in a clinical setting.

Therefore, it would be of great benefit to improve upon the prior art oligonucleotides by designing oligonucleotides that have improved delivery properties in vivo and are clinically meaningful.

SUMMARY OF INVENTION

Described herein are asymmetric chemically modified nucleic acid molecules with minimal double stranded regions, and the use of such molecules in gene silencing. RNAi molecules associated with the invention contain single stranded regions and double stranded regions, and can contain a variety of chemical modifications within both the single stranded and double stranded regions of the molecule. Additionally, the RNAi molecules can be attached to a hydrophobic conjugate such as a conventional and advanced sterol-type molecule. This new class of RNAi molecules has superior efficacy both in vitro and in vivo than previously described RNAi molecules.

Aspects of the invention relate to asymmetric nucleic acid molecules including a guide strand, with a minimal length of 16 nucleotides, and a passenger strand forming a double stranded nucleic acid, having a double stranded region and a single stranded region, the double stranded region having 8-15 nucleotides in length, the single stranded region having 5-12 nucleotides in length, wherein the passenger strand is linked to a lipophilic group, wherein at least 40% of the nucleotides of the double stranded nucleic acid are modified, and wherein the single stranded region has at least 2 phosphorothioate modifications. In some embodiments position 1 of the guide strand is 5' phosphorylated. In certain embodiments, position 1 of the guide strand is 2'O-methyl modified and 5' phosphorylated.

Aspects of the invention relate to isolated double stranded nucleic acid molecules including a longer strand of 15-21 nucleotides in length that has complementarily to a miRNA sequence, a shorter strand of 8-15 nucleotides in length linked at the 3' end to a lipophilic group, wherein the longer strand and the passenger strand form the double stranded nucleic acid molecule having a double stranded region and a single stranded region, wherein the longer strand has a 3' single stranded region of 2-13 nucleotides in length, comprising at least two phosphorothioate modification, and at least 50% nucleotides are modified.

Further aspects of the invention relate to isolated double stranded nucleic acid molecules including a guide strand of 17-21 nucleotides in length that has complementarity to a target gene, a passenger strand of 8-16 nucleotides in length linked at the 3' end to a lipophilic group, wherein the guide strand and the passenger strand form the double stranded nucleic acid molecule having a double stranded region and a single stranded region, wherein the guide strand has a 3' single stranded region of 2-13 nucleotides in length, each nucleotide within the single stranded region having a phosphorothioate modification, wherein the guide strand has a 5' phosphate modification and wherein at least 50% of C and U nucleotides in the double stranded region include at least one 2' O-methyl modification or 2'-fluoro modification.

In another aspect, the invention is an isolated double stranded nucleic acid molecule having a guide strand of 17-21 nucleotides in length that has complementarity to a target gene, a passenger strand of 10-16 nucleotides in length linked at the 3' end to a lipophilic group, wherein the guide strand and the passenger strand form the double stranded nucleic acid molecule having a double stranded region and a single stranded region, wherein the guide strand has a 3' single stranded region of 5-11 nucleotides in length, at least two nucleotide within the single stranded region having a phosphorothioate modification, wherein the guide strand has a 5' phosphate modification and wherein at least 50% of C and U nucleotides in the double stranded region are 2' O-methyl modification or 2'-fluoro modified.

The invention in another aspect is an isolated double stranded nucleic acid molecule having a guide strand of 17-21 nucleotides in length that has complementarity to a target gene, a passenger strand of 8-16 nucleotides in length linked at the 3' end to a lipophilic group, wherein the guide strand and the passenger strand form the double stranded nucleic acid molecule having a double stranded region and a single stranded region, wherein the guide strand has a 3' single stranded region of 6-8 nucleotides in length, each nucleotide within the single stranded region having a phosphorothioate modification, wherein the guide strand has a 5' phosphate modification, wherein the passenger strand includes at least two phosphorothioate modifications, wherein at least 50% of C and U nucleotides in the double stranded region include a 2' O-methyl modification or 2'-fluoro modification, and wherein the double stranded nucleic acid molecule has one end that is blunt or includes a one-two nucleotide overhang.

An isolated double stranded nucleic acid molecule having a guide strand of 17-21 nucleotides in length that has complementarity to a target gene, a passenger strand of 8-16 nucleotides in length linked at the 3' end to a lipophilic group, wherein the guide strand and the passenger strand form the double stranded nucleic acid molecule having a double stranded region and a single stranded region, wherein the guide strand has a 3' single stranded region, each nucleotide within the single stranded region having a phosphorothioate modification, wherein the guide strand has a 5' phosphate modification, wherein every C and U nucleotide in position 11-18 of the guide strand has a 2' O-methyl modification, wherein every nucleotide of the passenger strand is 2' O-methyl modified, and wherein the double stranded nucleic acid molecule has one end that is blunt or includes a one-two nucleotide overhang is provided in other aspects of the invention.

In another aspect the invention is an isolated double stranded nucleic acid molecule having a guide strand of 17-21 nucleotides in length that has complementarity to a target gene, a passenger strand of 8-15 nucleotides in length linked at the 3' end to a lipophilic group, wherein the lipophilic group is selected from the group consisting of cholesterol and a sterol type molecule with C17 polycarbon chain of 5-7 or 9-18 carbons in length, wherein the guide strand and the passenger strand form the double stranded nucleic acid molecule having a double stranded region and a single stranded region, wherein the guide strand has a 3' single stranded region, each nucleotide within the single stranded region having a phosphorothioate modification, wherein the guide strand has a 5' phosphate modification, wherein every C and U nucleotide in position 11-18 of the guide strand has a 2' O-methyl modification, wherein every C and U nucleotide in position 2-10 of the guide strand has a 2'F modification, wherein every nucleotide of the passenger strand is 2' O-methyl modified, and wherein the double stranded nucleic acid molecule has one end that is blunt or includes a one-two nucleotide overhang.

In yet another aspect the invention is an isolated nucleic acid molecule having a guide sequence that has complementarity to a target gene, a passenger sequence linked at the 3' end to a lipophilic group, wherein the guide sequence and the passenger sequence form a nucleic acid molecule having a double stranded region and a single stranded region, wherein the guide sequence has a 3' single stranded region of 2-13 nucleotides in length, each nucleotide within the single stranded region having a phosphorothioate modification, wherein the guide sequence has a 5' phosphate modification, wherein at least 50% of C and U nucleotides in the double stranded region include at least one 2' O-methyl modification or 2'-fluoro modification, and wherein the double stranded nucleic acid molecule has one end that is blunt or includes a one-two nucleotide overhang.

An isolated double stranded nucleic acid molecule having a guide strand and a passenger strand, wherein the region of the molecule that is double stranded is from 8-14 nucleotides long, wherein the guide strand contains a single stranded region that is 4-12 nucleotides long, and wherein the single stranded region of the guide strand contains 2-12 phosphorothioate modifications is provided in other aspects of the invention.

In some embodiments the guide strand contains 6-8 phosphorothioate modifications. In other embodiments the single stranded region of the guide strand is 6 nucleotides long.

In yet other embodiments the double stranded region is 13 nucleotides long. Optionally the double stranded nucleic acid molecule has one end that is blunt or includes a one-two nucleotide overhang.

In another aspect the invention is an isolated double stranded nucleic acid molecule having a guide strand, wherein the guide strand is 16-28 nucleotides long and has complementarity to a target gene, wherein the 3' terminal 10 nucleotides of the guide strand include at least two phosphate modifications, and wherein the guide strand has a 5' phosphate modification and includes at least one 2' O-methyl modification or 2'-fluoro modification, and a passenger strand, wherein the passenger strand is 8-14 nucleotides long and has complementarity to the guide strand, wherein the passenger strand is linked to a lipophilic group, wherein the guide strand and the passenger strand form the double stranded nucleic acid molecule.

In some embodiments the nucleotide in position one of the guide strand or sequence has a 2'-O-methyl modification. In other embodiments at least one C or U nucleotide in positions 2-10 of the guide strand or sequence has a 2'-fluoro modification. In yet other embodiments every C and U nucleotide in positions 2-10 of the guide strand or sequence has a 2'-fluoro modification. At least one C or U nucleotide in positions 11-18 of the guide strand or sequence may have a 2'-O-methyl modification. In some embodiments every C and U nucleotide in positions 11-18 of the guide strand or sequence has a 2'-O-methyl modification.

In yet other embodiments the 3' terminal 10 nucleotides of the guide strand include at least four phosphate modifications. Optionally the 3' terminal 10 nucleotides of the guide strand include at least eight phosphate modifications. In some embodiments the guide strand includes 4-14 phosphate modifications. In other embodiments the guide strand includes 4-10 phosphate modifications. In yet other embodiments the 3' terminal 6 nucleotides of the guide strand all include phosphate modifications. The phosphate modifications may be phosphorothioate modifications.

In some embodiments every C and U nucleotide on the passenger strand has a 2'-O-methyl modification. In other embodiments every nucleotide on the passenger strand has a 2'-O-methyl modification. In an embodiment at least one nucleotide on the passenger strand is phosphorothioate modified. At least two nucleotides on the passenger strand are phosphorothioate modified in other embodiments.

The lipophilic molecule may be a sterol, such as cholesterol.

In some embodiments the guide strand is 18-19 nucleotides long. In other embodiments the passenger strand is 11-13 nucleotides long.

The double stranded nucleic acid molecule has one end that is blunt or includes a one-two nucleotide overhang in other embodiments.

In other aspects the invention is an isolated double stranded nucleic acid molecule comprising a guide strand and a passenger strand, wherein the guide strand is from 16-29 nucleotides long and is substantially complementary to a target gene, wherein the passenger strand is from 8-14 nucleotides long and has complementarity to the guide strand, and wherein the guide stand has at least two chemical modifications. In some embodiments the at least two chemical modifications include at least two phosphorothioate modifications. In some embodiments the double stranded nucleic acid molecule has one end that is blunt or includes a one-two nucleotide overhang.

In some aspects the invention is an isolated double stranded nucleic acid molecule comprising a guide strand and a passenger strand, wherein the guide strand is from 16-29 nucleotides long and is substantially complementary to a target gene, wherein the passenger strand is from 8-14 nucleotides long and has complementarity to the guide strand, and wherein the guide stand has a single stranded 3' region that is 5 nucleotides or longer and a 5' region that is 1 nucleotide or less. The single stranded region may contain at least 2 phosphorothioate modifications.

An isolated double stranded nucleic acid molecule having a guide strand and a passenger strand, wherein the guide strand is from 16-29 nucleotides long and is substantially complementary to a target gene, wherein the passenger strand is from 8-16 nucleotides long and has complementarity to the guide strand, and wherein the guide stand has a single stranded 3' region that is 5 nucleotides or longer and a passenger strand has a sterol type molecule with C17 attached chain longer than 9 is provided in other aspects of the invention.

A duplex polynucleotide is provided in other aspects of the invention. The polynucleotide has a first polynucleotide wherein said first polynucleotide is complementary to a second polynucleotide and a target gene; and a second polynucleotide wherein said second polynucleotide is at least 6 nucleotides shorter than said first polynucleotide, wherein said first polynucleotide includes a single stranded region containing modifications selected from the group consisting of 40-90% hydrophobic base modifications, 40-90% phosphorothioates, and 40-90% modifications of the ribose moiety, or any combination thereof.

In other aspects the invention is a duplex polynucleotide having a first polynucleotide wherein said first polynucleotide is complementary to a second polynucleotide and a target gene; and a second polynucleotide wherein said second polynucleotide is at least 6 nucleotides shorter than said first polynucleotide, wherein the duplex polynucleotide includes a mismatch between nucleotides 9, 11, 12, 13 or 14 on the first polynucleotide and the opposite nucleotide on the second polynucleotide.

In other aspects the invention is a method for inhibiting the expression of a target gene in a mammalian cell, comprising contacting the mammalian cell with an isolated double stranded nucleic acid molecule of any one of claims **1**-**41** or a duplex polynucleotide of claim **43** or **44**.

A method of inducing RNAi in a subject is provided in other aspects of the invention. The method involves administering to a subject an effective amount for inducing RNAi of an mRNA of a target gene, an isolated double stranded nucleic acid molecule of any one of claims **1**-**41** or a duplex polynucleotide of claim **43** or **44**. In other embodiment the subject is a human. In other embodiments the target gene is PPIB, MAP4K4, or SOD1.

In other aspects an isolated hydrophobic modified polynucleotide having a polynucleotide, wherein the polynucleotide is double stranded RNA, attached to a hydrophobic molecule, wherein the hydrophobic molecule is attached to a base, a ribose or a backbone of a non-terminal nucleotide and wherein the isolated double stranded nucleic acid molecule comprises a guide strand and a passenger strand, wherein the guide strand is from 16-29 nucleotides long and is substantially complementary to a target gene, wherein the passenger strand is from 8-14 nucleotides long and has complementarity to the guide strand is provided.

In one embodiment the hydrophobic molecule is attached to the guide strand of the double stranded RNA. In another embodiment the 3' terminal 10 nucleotides of the guide strand include at least two phosphate modifications, and wherein the guide strand has a 5' phosphate modification and includes at least one 2' O-methyl modification or 2'-fluoro modification. In yet another embodiment the hydrophobic molecule is attached to the passenger strand of the double stranded RNA.

The invention provides an isolated hydrophobic modified polynucleotide having a polynucleotide non-covalently complexed to a hydrophobic molecule, wherein the hydrophobic molecule is a polycationic molecule. In some embodiments the polycationic molecule is selected from the group consisting of protamine, arginine rich peptides, and spermine.

In other aspects the invention an isolated hydrophobic modified polynucleotide having a polynucleotide, wherein the polynucleotide is double stranded RNA, directly complexed to a hydrophobic molecule without a linker, wherein the hydrophobic molecule is not cholesterol.

A composition having a hydrophobic modified polynucleotide, wherein the polynucleotide is double stranded RNA, attached to a hydrophobic molecule, wherein the double stranded nucleic acid molecule comprises a guide strand and a passenger strand, wherein the guide strand is from 16-29 nucleotides long and is substantially complementary to a target gene, wherein the passenger strand is from 8-14 nucleotides long and has complementarity to the guide strand, wherein position 1 of the guide strand is 5' phosphorylated or has a 2' O-methyl modification, wherein at least 40% of the nucleotides of the double stranded nucleic acid are modified, and wherein the double stranded nucleic acid molecule has one end that is blunt or includes a one-two nucleotide overhang; a neutral fatty mixture; and optionally a cargo molecule, wherein the hydrophobic modified polynucleotide and the neutral fatty mixture forms a micelle is provided in other aspects of the invention.

In some embodiments the 3' end of the passenger strand is linked to the hydrophobic molecule. In other embodiments the composition is sterile. In yet other embodiments the neutral fatty mixture comprises a DOPC (dioleoylphosphatidylcholine). In further embodiments the neutral fatty mixture comprises a DSPC (distearoylphosphatidylcholine). The neutral fatty mixture further comprises a sterol such as cholesterol in other embodiments.

In yet other embodiments the composition includes at least 20% DOPC and at least 20% cholesterol. The hydrophobic portion of the hydrophobic modified polynucleotide is a sterol in other embodiments. The sterol may be a cholesterol, a cholesteryl or modified cholesteryl residue. In other embodiments the hydrophobic portion of the hydrophobic modified polynucleotide is selected from the group consisting of bile acids, cholic acid or taurocholic acid, deoxycholate, oleyl litocholic acid, oleoyl cholenic acid, glycolipids, phospholipids, sphingolipids, isoprenoids, vitamins, saturated fatty acids, unsaturated fatty acids, fatty acid esters, triglycerides, pyrenes, porphyrines, Texaphyrine, adamantane, acridines, biotin, coumarin, fluorescein, rhodamine, Texas-Red, digoxygenin, dimethoxytrityl, t-butyldimethylsilyl, t-butyldiphenylsilyl, cyanine dyes (e.g. Cy3 or Cy5), Hoechst 33258 dye, psoralen, and ibuprofen.

In yet other embodiments the hydrophobic portion of the hydrophobic modified polynucleotide is a polycationic molecule, such as, for instance, protamine, arginine rich peptides, and/or spermine.

The composition optionally includes a cargo molecule such as a lipid, a peptide, vitamin, and/or a small molecule. In some embodiments the cargo molecule is a commercially available fat emulsions available for a variety of purposes selected from the group consisting of parenteral feeding. In some embodiments the commercially available fat emulsion is an intralipid or a nutralipid. In other embodiments the cargo molecule is a fatty acid mixture containing more then 74% of linoleic acid, a fatty acid mixture containing at least 6% of cardiolipin, or a fatty acid mixture containing at least 74% of linoleic acid and at least 6% of cardiolipin. In another embodiment the cargo molecule is a fusogenic lipid, such as for example, DOPE, and preferably is at least 10% fusogenic lipid

In some embodiments the polynucleotide includes chemical modifications. For instance it may be at least 40% modified.

A method of inducing RNAi in a subject is provided in another aspect of the invention. The method involves administering to a subject an effective amount for inducing RNAi of mRNA of a target gene, an isolated double stranded nucleic acid molecule or a duplex polynucleotide or a composition of the invention, wherein the polynucleotide has at least a region of sequence correspondence to the target gene, wherein the step of administering is systemic, intravenous, intraperitoneal, intradermal, topical, intranasal, inhalation, oral, intramucosal, local injection, subcutaneous, oral tracheal, or intraocular.

In other embodiment the subject is a human. In other embodiments the target gene is PPIB, MAP4K4, or SOD1.

In some aspects the invention is a single-stranded RNA of less than 35 nucleotides in length that forms a hairpin structure, said hairpin includes a double-stranded stem and a single-stranded loop, said double-stranded stem having a 5'-stem sequence having a 5'-end, and a 3'-stem sequence having a 3'-end; and said 5'-stem sequence and at least a portion of said loop form a guide sequence complementary to a transcript of a target gene, wherein said polynucleotide mediates sequence-dependent gene silencing of expression of said target gene, wherein each nucleotide within the single-stranded loop region has a phosphorothioate modification, and wherein at least 50% of C and U nucleotides in the double stranded region include a 2' O-methyl modification or 2'-fluoro modification. In one embodiment every C and U nucleotide in position 11-18 of the guide sequence has a 2' O-methyl modification.

A polynucleotide construct is provided in other aspects, the polynucleotide having two identical single-stranded polynucleotides, each of said single-stranded polynucleotide comprising a 5'-stem sequence having a 5'-end, a 3'-stem sequence having a 3'-end, and a linker sequence linking the 5'-stem sequence and the 3'-stem sequence, wherein: (1) the 5'-stem sequence of a first single-stranded polynucleotide hybridizes with the 3'-stem sequence of a second single-stranded polynucleotide to form a first double-stranded stem region; (2) the 5'-stem sequence of the second single-stranded polynucleotide hybridize with the 3'-stem sequence of the first single-stranded polynucleotide to form a second double-stranded stem region; and, (3) the linker sequences of the first and the second single-stranded polynucleotides form a loop or bulge connecting said first and said second double-stranded stem regions, wherein the 5'-stem sequence and at least a portion of the linker sequence form a guide sequence complementary to a transcript of a target gene, wherein said polynucleotide construct mediates sequence-dependent gene silencing of expression of said target gene, wherein each nucleotide within the single-stranded loop region has a phosphorothioate modification, and wherein at least 50% of C and U nucleotides in the double stranded regions include a 2' O-methyl modification or 2'-fluoro modification.

In one embodiment every C and U nucleotide in position 11-18 of the guide sequence has a 2' O-methyl modification.

In some embodiments, the guide strand is 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, or 29 nucleotides long. In some embodiments, the passenger strand is 8, 9, 10, 11, 12, 13 or 14 nucleotides long. In some embodiments, the nucleic acid molecule has a thermodynamic stability (ΔG) of less than −20 kkal/mol.

Aspects of the invention relate to nucleic acid molecules that are chemically modified. In some embodiments, the chemical modification is selected from the group consisting of 5' Phosphate, 2'-O-methyl, 2'-O-ethyl, 2'-fluoro, ribothymidine, C-5 propynyl-dC (pdC), C-5 propynyl-dU (pdU), C-5 propynyl-C (pC), C-5 propynyl-U (pU), 5-methyl C, 5-methyl U, 5-methyl dC, 5-methyl dU methoxy, (2,6-diaminopurine), 5'-Dimethoxytrityl-N4-ethyl-2'-deoxyCytidine, C-5 propynyl-fC (pfC), C-5 propynyl-fU (pfU), 5-methyl fC, 5-methyl fU, C-5 propynyl-mC (pmC), C-5 propynyl-fU (pmU), 5-methyl mC, 5-methyl mU, LNA (locked nucleic acid), MGB (minor groove binder) and other base modifications which increase base hydrophobicity. More than one chemical modification may be present in the same molecule. In some embodiments, chemical modification increases stability and/or improves thermodynamic stability (ΔG). In some embodiments, at least 90% of CU residues on a nucleic acid molecule are modified.

In some embodiments, the nucleotide in position one of the guide strand has a 2'-O-methyl modification and/or a 5' Phosphate modification. In some embodiments, at least one C or U nucleotide in positions 2-10 of the guide strand has a 2'-fluoro modification. In certain embodiments, every C and U nucleotide in positions 2-10 of the guide strand has a 2'-fluoro modification. In some embodiments, at least one C or U nucleotide in positions 11-18 of the guide strand has a 2'-O-methyl modification. In certain embodiments, every C and U nucleotide in positions 11-18 of the guide strand has a 2'-O-methyl modification. In some embodiments, every C and U nucleotide on the passenger strand has a 2'-O-methyl modification. In certain embodiments, every nucleotide on the passenger strand has a 2'-O-methyl modification.

In some embodiments, nucleic acid molecules associated with the invention contain a stretch of at least 4 nucleotides that are phosphorothioate modified. In certain embodiments, the stretch of nucleotides that are phosphorothioate modified is at least 12 nucleotides long. In some embodiments, the stretch of nucleotides that are phosphorothioate modified is not fully single stranded.

Nucleic acid molecules associated with the invention may be attached to a conjugate. In some embodiments, the conjugate is attached to the guide strand, while in other embodiments the conjugate is attached to the passenger strand. In some embodiments, the conjugate is hydrophobic. In some embodiments, the conjugate is a sterol such as cholesterol. In some embodiments, nucleic acid molecules associated with the invention are blunt-ended.

Aspects of the invention relate to double stranded nucleic acid molecule including a guide strand and a passenger strand, wherein the region of the molecule that is double stranded is from 8-14 nucleotides long, and wherein the molecule has a thermodynamic stability (ΔG) of less than −13 kkal/mol.

In some embodiments, the region of the molecule that is double stranded is 8, 9, 10, 11, 12, 13, or 14 nucleotides long. In some embodiments, the molecule has a thermodynamic stability (ΔG) of less than −20 kkal/mol. The nucleic acid molecules, in some embodiments are chemically modified. In certain embodiments, the chemical modification is selected from the group consisting of 5' Phosphate, 2'-O-methyl, 2'-β-ethyl, 2'-fluoro, ribothymidine, C-5 propynyl-dC (pdC), C-5 propynyl-dU (pdU), C-5 propynyl-C (pC), C-5 propynyl-U (pU), 5-methyl C, 5-methyl U, 5-methyl dC, 5-methyl dU methoxy, (2,6-diaminopurine), 5'-Dimethoxytrityl-N4-ethyl-2'-deoxyCytidine, C-5 propynyl-fC (pfC), C-5 propynyl-fU (pfU), 5-methyl fC, 5-methyl fU, C-5 propynyl-mC (pmC), C-5 propynyl-fU (pmU), 5-methyl mC, 5-methyl mU, LNA (locked nucleic acid), MGB (minor groove binder) and other base modifications which increase base hydrophobicity. More than one chemical modification may be present in the same molecule. In some embodiments, chemical modification increases stability and/or improves thermodynamic stability (ΔG). In some embodiments, at least 90% of CU residues on a nucleic acid molecule are modified.

In some embodiments, the nucleotide in position one of the guide strand has a 2'-O-methyl modification and/or a 5' Phosphate modification. In some embodiments, at least one C or U nucleotide in positions 2-10 of the guide strand has a 2'-fluoro modification. In certain embodiments, every C and U nucleotide in positions 2-10 of the guide strand has a 2'-fluoro modification. In some embodiments, at least one C or U nucleotide in positions 11-18 of the guide strand has a 2'-O-methyl modification. In certain embodiments, every C and U nucleotide in positions 11-18 of the guide strand has a 2'-O-methyl modification. In some embodiments, every C and U nucleotide on the passenger strand has a 2'-O-methyl modification. In certain embodiments, every nucleotide on the passenger strand has a 2'-O-methyl modification.

The nucleic acid molecules associated with the invention may contain a stretch of at least 4 nucleotides that are phosphorothioate modified. In certain embodiments, the stretch of nucleotides that are phosphorothioate modified is at least 12 nucleotides long. In some embodiments, the stretch of nucleotides that are phosphorothioate modified is not fully single stranded. In some embodiments, the nucleic acid molecules are attached to a conjugate. In some embodiments, the conjugate is attached to the guide strand, while in other embodiments the conjugate is attached to the passenger strand. In some embodiments, the conjugate is hydrophobic. In some embodiments, the conjugate is a sterol such as cholesterol. In some embodiments, nucleic acid molecules associated with the invention are blunt-ended. In some embodiments, the nucleic acid molecules are blunt ended at the 5' end. In certain embodiments, the nucleic acid molecules are blunt ended at the 5' end where the region of complementarity between the two strands of the molecule begins.

Aspects of the invention relate to methods for inhibiting the expression of a target gene in a mammalian cell. Methods include contacting the mammalian cell with an isolated double stranded nucleic acid molecule including a guide strand and a passenger strand, wherein the guide strand is from 16-29 nucleotides long and has complementarity to a target gene, wherein the passenger strand is from 8-14 nucleotides long and has complementarity to the guide strand, and wherein the double stranded nucleic acid molecule has a thermodynamic stability (ΔG) of less than −13 kkal/mol.

The cell may be contacted in vivo or in vitro. In some embodiments, the guide strand is 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, or 29 nucleotides long. In some embodiments, the passenger strand is 8, 9, 10, 11, 12, 13 or 14 nucleotides long. In some embodiments, the nucleic acid molecule has a thermodynamic stability (ΔG) of less than −20 kkal/mol.

The nucleic acid molecules associated with methods described herein may be chemically modified. In some embodiments, the chemical modification is selected from the group consisting of 5' Phosphate, 2'-O-methyl, 2'-O-ethyl, 2'-fluoro, ribothymidine, C-5 propynyl-dC (pdC), C-5 propynyl-dU (pdU), C-5 propynyl-C (pC), C-5 propynyl-U (pU), 5-methyl C, 5-methyl U, 5-methyl dC, 5-methyl dU methoxy, (2,6-diaminopurine), 5'-Dimethoxytrityl-N4-ethyl-2'-deoxyCytidine, C-5 propynyl-fC (pfC), C-5 propynyl-fU (pfU), 5-methyl fC, 5-methyl fU, C-5 propynyl-mC (pmC), C-5 propynyl-fU (pmU), 5-methyl mC, 5-methyl mU, LNA (locked nucleic acid), MGB (minor groove binder) and other base modifications which increase base hydrophobicity. More than one chemical modification may be present in the same molecule. In some embodiments, chemical modification increases stability and/or improves thermodynamic stability (ΔG). In some embodiments, at least 90% of CU residues on a nucleic acid molecule are modified.

In some embodiments, the nucleotide in position one of the guide strand has a 2'-O-methyl modification and/or a 5' Phosphate modification. In some embodiments, at least one C or U nucleotide in positions 2-10 of the guide strand has a 2'-fluoro modification. In certain embodiments, every C and U nucleotide in positions 2-10 of the guide strand has a 2'-fluoro modification. In some embodiments, at least one C or U nucleotide in positions 11-18 of the guide strand has a 2'-O-methyl modification. In certain embodiments, every C and U nucleotide in positions 11-18 of the guide strand has a 2'-O-methyl modification. In some embodiments, every C and U nucleotide on the passenger strand has a 2'-O-methyl modification. In certain embodiments, every nucleotide on the passenger strand has a 2'-O-methyl modification.

In some embodiments, nucleic acid molecules associated with the invention contain a stretch of at least 4 nucleotides that are phosphorothioate modified. In certain embodiments, the stretch of nucleotides that are phosphorothioate modified is at least 12 nucleotides long. In some embodiments, the stretch of nucleotides that are phosphorothioate modified is not fully single stranded.

Nucleic acid molecules associated with the invention may be attached to a conjugate. In some embodiments, the conjugate is attached to the guide strand, while in other embodiments the conjugate is attached to the passenger strand. In some embodiments, the conjugate is hydrophobic. In some embodiments, the conjugate is a sterol such as cholesterol. In some embodiments, nucleic acid molecules associated with the invention are blunt-ended.

Methods for inhibiting the expression of a target gene in a mammalian cell described herein include contacting the mammalian cell with an isolated double stranded nucleic acid molecule including a guide strand and a passenger strand, wherein the region of the molecule that is double stranded is from 8-14 nucleotides long, and wherein the molecule has a thermodynamic stability (ΔG) of less than −13 kkal/mol.

In some embodiments, the region of the molecule that is double stranded is 8, 9, 10, 11, 12, 13, or 14 nucleotides long. In some embodiments, the molecule has a thermodynamic stability (ΔG) of less than −20 kkal/mol. The nucleic acid molecules, in some embodiments are chemically modified. In certain embodiments, the chemical modification is selected from the group consisting of 5' Phosphate, 2'-O-methyl, 2'-β-ethyl, 2'-fluoro, ribothymidine, C-5 propynyl-dC (pdC), C-5 propynyl-dU (pdU), C-5 propynyl-C (pC), C-5 propynyl-U (pU), 5-methyl C, 5-methyl U, 5-methyl dC, 5-methyl dU methoxy, (2,6-diaminopurine), 5'-Dimethoxytrityl-N4-ethyl-2'-deoxyCytidine, C-5 propynyl-fC (pfC), C-5 propynyl-fU (pfU), 5-methyl fC, 5-methyl fU, C-5 propynyl-mC (pmC), C-5 propynyl-fU (pmU), 5-methyl mC, 5-methyl mU, LNA (locked nucleic acid), MGB (minor groove binder) and other base modifications which increase base hydrophobicity. More than one chemical modification may be present in the same molecule. In some embodiments, chemical modification increases stability and/or improves thermodynamic stability (ΔG). In some embodiments, at least 90% of CU residues on a nucleic acid molecule are modified.

In some embodiments, the nucleotide in position one of the guide strand has a 2'-O-methyl modification and/or a 5' Phosphate modification. In some embodiments, at least one C or U nucleotide in positions 2-10 of the guide strand has a 2'-fluoro modification. In certain embodiments, every C and U nucleotide in positions 2-10 of the guide strand has a 2'-fluoro modification. In some embodiments, at least one C or U nucleotide in positions 11-18 of the guide strand has a 2'-O-methyl modification. In certain embodiments, every C and U nucleotide in positions 11-18 of the guide strand has a 2'-O-methyl modification. In some embodiments, every C and U nucleotide on the passenger strand has a 2'-O-methyl modification. In certain embodiments, every nucleotide on the passenger strand has a 2'-O-methyl modification.

The nucleic acid molecules associated with the invention may contain a stretch of at least 4 nucleotides that are phosphorothioate modified. In certain embodiments, the stretch of nucleotides that are phosphorothioate modified is at least 12 nucleotides long. In some embodiments, the stretch of nucleotides that are phosphorothioate modified is not fully single stranded. In some embodiments, the nucleic acid molecules are attached to a conjugate. In some embodiments, the conjugate is attached to the guide strand, while in other embodiments the conjugate is attached to the passenger strand. In some embodiments, the conjugate is hydrophobic. In some embodiments, the conjugate is a sterol such as cholesterol. In some embodiments, nucleic acid molecules associated with the invention are blunt-ended.

In another embodiment, the invention provides a method for selecting an siRNA for gene silencing by (a) selecting a target gene, wherein the target gene comprises a target sequence; (b) selecting a candidate siRNA, wherein said candidate siRNA comprises a guide strand of 16-29 nucleotide base pairs and a passenger strand of 8-14 nucleotide base pairs that form a duplex comprised of an antisense region and a sense region and said antisense region of said candidate siRNA is at least 80% complementary to a region of said target sequence; (c) determining a thermodynamic stability (ΔG) of the candidate siRNA; and (e) selecting said candidate siRNA as an siRNA for gene silencing, if said thermodynamic stability is less than −13 kkal/mol.

Aspects of the invention relate to isolated double stranded nucleic acid molecules including a guide strand and a passenger strand, wherein the guide strand is 18-19 nucleotides long and has complementarity to a target gene, wherein the passenger strand is 11-13 nucleotides long and has complementarity to the guide strand, and wherein the double stranded nucleic acid molecule has a thermodynamic stability (ΔG) of less than −13 kkal/mol.

In some embodiments, the nucleotide in position one of the guide strand has a 2'-O-methyl modification and/or a 5' Phosphate modification. In some embodiments, at least one C or U nucleotide in positions 2-10 of the guide strand has a 2'-fluoro modification. In certain embodiments, every C and U nucleotide in positions 2-10 of the guide strand has a 2'-fluoro modification. In some embodiments, at least one C or U nucleotide in positions 11-18 of the guide strand has a 2'-O-methyl modification. In certain embodiments, every C and U nucleotide in positions 11-18 of the guide strand has a 2'-O-methyl modification.

In some embodiments, the guide strand contains a stretch of at least 4 nucleotides that are phosphorothioate modified. In certain embodiments, the guide strand contains a stretch of at least 8 nucleotides that are phosphorothioate modified. In some embodiments, every C and U nucleotide on the passenger strand has a 2'-O-methyl modification. In certain embodiments, every nucleotide on the passenger strand has a 2'-O-methyl modification. In some embodiments, at least one, or at least two nucleotides on the passenger strand is phosphorothioate modified. The nucleic acid molecule can be attached to a conjugate on either the guide or passenger strand. In some embodiments, the conjugate is a sterol such as cholesterol.

Aspects of the invention relate to isolated double stranded nucleic acid molecules including a guide strand, wherein the guide strand is 16-28 nucleotides long and has complementarity to a target gene, wherein the 3' terminal 10 nucleotides of the guide strand include at least two phosphate modifications, and wherein the guide strand includes at least one 2' O-methyl modification or 2'-fluoro modification, and a passenger strand, wherein the passenger strand is 8-28 nucleotides long and has complementarity to the guide strand, wherein the passenger strand is linked to a lipophilic group, wherein the guide strand and the passenger strand form the double stranded nucleic acid molecule.

In some embodiments, the nucleotide in position one of the guide strand has a 2'-O-methyl modification and/or a 5' Phosphate modification. In some embodiments, at least one C or U nucleotide in positions 2-10 of the guide strand has a 2'-fluoro modification. In certain embodiments, every C and U nucleotide in positions 2-10 of the guide strand has a 2'-fluoro modification. In some embodiments, at least one C or U nucleotide in positions 11-18 of the guide strand has a 2'-O-methyl modification. In certain embodiments, every C and U nucleotide in positions 11-18 of the guide strand has a 2'-O-methyl modification.

In some embodiments, the 3' terminal 10 nucleotides of the guide strand include at least four, or at least eight phosphate modifications. In certain embodiments, the guide strand includes 2-14 or 4-10 phosphate modifications. In some embodiments, the 3' terminal 6 nucleotides of the guide strand all include phosphate modifications. In certain embodiments, the phosphate modifications are phosphorothioate modifications.

In some embodiments, every C and U nucleotide on the passenger strand has a 2'-O-methyl modification. In certain embodiments, every nucleotide on the passenger strand has a 2'-O-methyl modification. In some embodiments, at least one, or at least two nucleotides on the passenger strand is phosphorothioate modified. In some embodiments, the lipophilic molecule is a sterol such as cholesterol. In some embodiments, the guide strand is 18-19 nucleotides long and the passenger strand is 11-13 nucleotides long.

Aspects of the invention relate to isolated double stranded nucleic acid molecules including a guide strand and a passenger strand, wherein the guide strand is from 16-29 nucleotides long and is substantially complementary to a target gene, wherein the passenger strand is from 8-14 nucleotides long and has complementarity to the guide strand, and wherein the guide stand has at least two chemical modifications. In some embodiments, the two chemical modifications are phosphorothioate modifications.

Further aspects of the invention relate to isolated double stranded nucleic acid molecule comprising a guide strand and a passenger strand, wherein the guide strand is from 16-29 nucleotides long and is substantially complementary to a target gene, wherein the passenger strand is from 8-14 nucleotides long and has complementarity to the guide strand, and wherein the guide stand has a single stranded 3' region that is 5 nucleotides or longer. In some embodiments, the single stranded region contains at least 2 phosphorothioate modifications.

Further aspects of the invention relate to isolated double stranded nucleic acid molecules including a guide strand and a passenger strand, wherein the guide strand is from 18-21 nucleotides long and is substantially complementary to a target gene, wherein the passenger strand is from 11-14 nucleotides long and has complementarity to the guide strand, and wherein position one of the guide stand has 2-OMe and 5' phosphate modifications, every C and U in positions 2 to 11 of the guide strand are 2-F modified, every C and U in positions 12-18 of the guide strand are 2'OMe modified, and 80% of Cs and Us on the passenger strand are 2'OMe modified

Another aspect of the invention relates to isolated double stranded nucleic acid molecules including a guide strand and a passenger strand, wherein the guide strand is from 18-21 nucleotides long and is substantially complementary to a target gene, wherein the passenger strand is from 11-14 nucleotides long and has complementarity to the guide strand, and wherein the guide stand has 2-OMe and 5' phosphate modifications at position 1, every C and U in positions 2 to 11 of the guide strand are 2-F modified, every C and U in positions 12-18 of the guide strand are 2'OMe modified, 80% of Cs and Us on the passenger strand are 2'OMe and the 3' end of the passenger strand is attached to a conjugate. In some embodiments the conjugate is selected from sterols, sterol-type molecules, hydrophobic vitamins or fatty acids.

Each of the limitations of the invention can encompass various embodiments of the invention. It is, therefore, anticipated that each of the limitations of the invention involving any one element or combinations of elements can be included in each aspect of the invention. This invention is not limited in its application to the details of construction and the arrangement of components set forth in the following description or illustrated in the drawings. The invention is capable of other embodiments and of being practiced or of being carried out in various ways.

BRIEF DESCRIPTION OF DRAWINGS

The accompanying drawings are not intended to be drawn to scale. In the drawings, each identical or nearly identical component that is illustrated in various figures is represented by a like numeral. For purposes of clarity, not every component may be labeled in every drawing. In the drawings:

FIG. **1** is a schematic depicting proposed structures of asymmetric double stranded RNA molecules (adsRNA). Bold lines represent sequences carrying modification patterns compatible with RISC loading. Striped lines represent polynucleotides carrying modifications compatible with passenger strands. Plain lines represent a single stranded polynucleotide with modification patterns optimized for cell interaction and uptake. FIG. **1**A depicts adsRNA with extended guide or passenger strands; FIG. **1**B depicts adsRNA with length variations of a cell penetrating polynucleotide; FIG. **1**C depicts adsRNA with 3' and 5' conjugates; FIG. **1**D depicts adsRNAs with mismatches.

FIG. **2** is a schematic depicting asymmetric dsRNA molecules with different chemical modification patterns. Several examples of chemical modifications that might be used to increase hydrophobicity are shown including 4-pyridyl, 2-pyridyl, isobutyl and indolyl based position 5 uridine modifications.

FIG. **3** is a schematic depicting the use of dsRNA binding domains, protamine (or other Arg rich peptides), spermidine or similar chemical structures to block duplex charge to facilitate cellular entry.

FIG. **4** is a schematic depicting positively charged chemicals that might be used for polynucleotide charge blockage.

FIG. **5** is a schematic depicting examples of structural and chemical compositions of single stranded RISC entering polynucleotides. The combination of one or more modifications including 2' d, 2'Ome, 2'F, hydrophobic and phosphorothioate modifications can be used to optimize single strand entry into the RISC.

FIG. **6** is a schematic depicting examples of structural and chemical composition of RISC substrate inhibitors. Combinations of one or more chemical modifications can be used to mediate efficient uptake and efficient binding to preloaded RISC complex.

FIG. **7** is a schematic depicting structures of polynucleotides with sterol type molecules attached, where R represent a polycarbonic tail of 9 carbons or longer. FIG. **7**A depicts an adsRNA molecule; FIG. **7**B depicts an siRNA molecule of approximately 17-30 bp long; FIG. **7**C depicts a RISC entering strand; FIG. **7**D depicts a substrate analog strand. Chemical modification patterns, as depicted in FIG. **7**, can be optimized to promote desired function.

FIG. **8** is a schematic depicting examples of naturally occurring phytosterols with a polycarbon chain that is longer than 8, attached at position 17. More than 250 different types of phytosterols are known.

FIG. **9** is a schematic depicting examples of sterol-like structures, with variations in the size of the polycarbon chains attached at position 17.

FIG. **10** presents schematics and graphs demonstrating that the percentage of liver uptake and plasma clearance of lipid emulsions containing sterol type molecules is directly affected by the size of the polycarbon chain attached at position 17. This figure is adapted from Martins et al, Journal of Lipid Research (1998).

FIG. **11** is a schematic depicting micelle formation. FIG. **11**A depicts a polynucleotide with a hydrophobic conjugate; FIG. **11**B depicts linoleic acid; FIG. **11**C depicts a micelle formed from a mixture of polynucleotides containing hydrophobic conjugates combined with fatty acids.

FIG. **12** is a schematic depicting how alteration in lipid composition can affect pharmacokinetic behavior and tissue distribution of hydrophobically modified and/or hydrophobically conjugated polynucleotides. In particular, use of lipid mixtures enriched in linoleic acid and cardiolipin results in preferential uptake by cardiomyocites.

FIG. **13** is a schematic showing examples of RNAi constructs and controls used to target MAP4K4 expression. RNAi construct 12083 corresponds to SEQ ID NOs:597 and 598. RNAi construct 12089 corresponds to SEQ ID NO:599.

FIG. **14** is a graph showing MAP4K4 expression following transfection with RNAi constructs associated with the invention. RNAi constructs tested were: 12083 (Nicked), 12085 (13 nt Duplex), 12089 (No Stem Pairing) and 12134 (13 nt miniRNA). Results of transfection were compared to an untransfected control sample. RNAi construct 12083 corresponds to SEQ ID NOs:597 and 598. RNAi construct 12085 corresponds to SEQ ID NOs:600 and 601. RNAi construct 12089 corresponds to SEQ ID NO:599. RNAi construct 12134 corresponds to SEQ ID NOs:602 and 603.

FIG. **15** is a graph showing expression of MAP4K4 24 hours post-transfection with RNAi constructs associated with the invention. RNAi constructs tested were: 11546 (MAP4K4 rxRNA), 12083 (MAP4K4 Nicked Construct), 12134 (12 bp soloRNA) and 12241 (14/3/14 soloRNA). Results of transfection were compared to a filler control sample. RNAi construct 11546 corresponds to SEQ ID NOs:604 and 605. RNAi construct 12083 corresponds to SEQ ID NOs:597 and 598. RNAi construct 12134 corresponds to SEQ ID NOs:602 and 603. RNAi construct 12241 corresponds to SEQ ID NOs:606 and 607.

FIG. **16** presents a graph and several tables comparing parameters associated with silencing of MAP4K4 expression following transfection with RNAi constructs associated with the invention. The rxRNA construct corresponds to SEQ ID NOs:604 and 605. The 14-3-14 soloRNA construct corresponds to SEQ ID NOs:606 and 607. The 13/19 duplex (nicked construct) corresponds to SEQ ID NOs:597 and 598. The 12-bp soloRNA construct corresponds to SEQ ID NOs: 602 and 603.

FIG. **17** is a schematic showing examples of RNAi constructs and controls used to target SOD1 expression. The 12084 RNAi construct corresponds to SEQ ID NOs:612 and 613.

FIG. **18** is a graph showing SOD1 expression following transfection with RNAi constructs associated with the invention. RNAi constructs tested were: 12084 (Nicked), 12086 (13 nt Duplex), 12090 (No Stem Pairing) and 12035 (13 nt MiniRNA). Results of transfection were compared to an untransfected control sample. The 12084 RNAi construct corresponds to SEQ ID NOs:612 and 613. The 12086 RNAi construct corresponds to SEQ ID NOs:608 and 609. The 12035 RNAi construct corresponds to SEQ ID NOs:610 and 611.

FIG. **19** is a graph showing expression of SOD1 24 hours post-transfection with RNAi constructs associated with the invention. RNAi constructs tested were: 10015 (SOD1 rxRNA) and 12084 (SOD1 Nicked Construct). Results of transfection were compared to a filler control sample. The 10015 RNAi construct corresponds to SEQ ID NOs:614 and 615. The 12084 RNAi construct corresponds to SEQ ID NOs: 612 and 613.

FIG. **20** is a schematic indicating that RNA molecules with double stranded regions that are less than 10 nucleotides are not cleaved by Dicer.

FIG. **21** is a schematic revealing a hypothetical RNAi model for RNA induced gene silencing.

FIG. **22** is a graph showing chemical optimization of asymmetric RNAi compounds. The presence of chemical modifications, in particular 2'F UC, phosphorothioate modifications on the guide strand, and complete CU 2'OMe modification of the passenger strands results in development of functional compounds. Silencing of MAP4K4 following lipid-mediated transfection is shown using RNAi molecules with specific modifications. RNAi molecules tested had sense strands that were 13 nucleotides long and contained the following modifications: unmodified; C and U 2'OMe; C and U 2'OMe and 3' Chl; rxRNA 2'OMe pattern; or full 2'OMe, except base 1. Additionally, the guide (anti-sense) strands of the RNAi molecules tested contained the following modifications: unmodified; unmodified with 5'P; C and U 2'F; C and U 2'F with 8 PS 3' end; and unmodified (17 nt length). Results for rxRNA 12/10 Duplex and negative controls are also shown.

FIG. **23** demonstrates that the chemical modifications described herein significantly increase in vitro efficacy in un-assisted delivery of RNAi molecules in HeLa cells. The structure and sequence of the compounds were not altered; only the chemical modification patterns of the molecules were modified. Compounds lacking 2' F, 2'O-me, phosphorothioate modification, or cholesterol conjugates were completely inactive in passive uptake. A combination of all 4 of these types of modifications produced the highest levels of activity (compound 12386).

FIG. **24** is a graph showing MAP4K4 expression in Hela cells following passive uptake transfection of: NT Accell modified siRNA, MAP4K4 Accell siRNA, Non-Chl nanoRNA (12379) and sd-nanoRNA (12386).

FIG. **25** is a graph showing expression of MAP4K4 in HeLa cells following passive uptake transfection of various concentrations of RNA molecules containing the following parameters: Nano Lead with no 3'Chl; Nano Lead; Accell MAP4K4; 21mer GS with 8 PS tail; 21mer GS with 12 PS tail; and 25mer GS with 12 PS tail.

FIG. **26** is a graph demonstrating that reduction in oligonucleotide content increases the efficacy of unassisted uptake. Similar chemical modifications were applied to assymetric compounds, traditional siRNA compounds and 25 mer RNAi compounds. The assymetric small compounds demonstrated the most significant efficacy.

FIG. **27** is a graph demonstrating the importance of phosphorothioate content for un-assisted delivery. FIG. **27**A demonstrates the results of a systematic screen that revealed that the presence of at least 2-12 phosphorothioates in the guide strand significantly improves uptake; in some embodiments, 4-8 phosphorothioate modifications were found to be preferred. FIG. **27** B reveals that the presence or absence of phosphorothioate modifications in the sense strand did not alter efficacy.

FIG. **28** is a graph showing expression of MAP4K4 in primary mouse hepatocytes following passive uptake transfection of: Accell Media-Ctrl-UTC; MM APOB Alnylam; Active APOB Alnylam; nanoRNA without chl; nanoRNA MAP4K4; Mouse MAP4K4 Accell Smartpool; DY547 Accell Control; Luc Ctrl rxRNA with Dy547; MAP4K4 rxRNA with DY547; and AS Strand Alone (nano).

FIG. **29** is a graph showing expression of ApoB in mouse primary hepatocytes following passive uptake transfection of: Accell Media-Ctrl-UTC; MM APOB Alnylam; Active APOB Alnylam; nanoRNA without chl; nanoRNA MAP4K4; Mouse MAP4K4 Accell Smartpool; DY547 Accell Control; Luc Ctrl rxRNA with Dy547; MAP4K4 rxRNA with DY547; and AS Strand Alone (nano).

FIG. **30** is a graph showing expression of MAP4K4 in primary human hepatocytes following passive uptake transfection of: 11550 MAP4K4 rxRNA; 12544 mM MAP4K4 nanoRNA; 12539 Active MAP4K4 nanoRNA; Accell Media; and UTC.

FIG. **31** is a graph showing ApoB expression in primary human hepatoctyes following passive uptake transfection of: 12505 Active ApoB chol-siRNA; 12506 mM ApoB chol-siRNA; Accell Media; and UTC.

FIG. **32** is an image depicting localization of sd-rxRNA^{nano} localization.

FIG. **33** is an image depicting localization of Chol-siRNA (Alnylam).

FIG. **34** is a schematic of 1st generation (G1) sd-rxRNA^{nano} molecules associated with the invention indicating regions that are targeted for modification, and functions associated with different regions of the molecules.

FIG. **35** depicts modification patterns that were screened for optimization of sd-rxRNA' (G1). The modifications that were screened included, on the guide strand, lengths of 19, 21 and 25 nucleotides, phosphorothioate modifications of 0-18 nucleotides, and replacement of 2'F modifications with 2'OMe, 5 Methyl C and/or ribo Thymidine modifications. Modifications on the sense strand that were screened included nucleotide lengths of 11, 13 and 19 nucleotides, phosphorothiote modifications of 0-4 nucleotides and 2'OMe modifications.

FIG. **36** is a schematic depicting modifications of sd-rxRNA^{nano} that were screened for optimization.

FIG. **37** is a graph showing percent MAP4K4 expression in Hek293 cells following transfection of: Risc Free siRNA; rxRNA; Nano (unmodified); GS alone; Nano Lead (no Chl); Nano (GS: (3) 2'OMe at positions 1, 18, and 19, 8 PS, 19 nt); Nano (GS: (3) 2'OMe at positions 1, 18, and 19, 8 PS, 21 nt); Nano (GS: (3) 2'OMe at positions 1, 18, and 19, 12 PS, 21 nt); and Nano (GS: (3) 2'OMe at positions 1, 18, and 19, 12 PS, 25 nt);

FIG. **38** is a graph showing percent MAP4K4 expression in HeLa cells following passive uptake transfection of: GS alone; Nano Lead; Nano (GS: (3) 2'OMe at positions 1, 18, and 19, 8 PS, 19 nt); Nano (GS: (3) 2'OMe at positions 1, 18, and 19, 8 PS, 21 nt); Nano (GS: (3) 2'OMe at positions 1, 18, and 19, 12 PS, 21 nt); Nano (GS: (3) 2'OMe at positions 1, 18, and 19, 12 PS, 25 nt).

FIG. **39** is a graph showing percent MAP4K4 expression in Hek293 cells following lipid mediated transfection of: Guide Strand alone (GS: 8 PS, 19 nt); Guide Strand alone (GS: 18 PS, 19 nt); Nano (GS: no PS, 19 nt); Nano (GS: 2 PS, 19 nt); Nano (GS: 4 PS, 19 nt); Nano (GS: 6 PS, 19 nt); Nano Lead (GS: 8 PS, 19 nt); Nano (GS: 10 PS, 19 nt); Nano (GS: 12 PS, 19 nt); and Nano (GS: 18 PS, 19 nt).

FIG. **40** is a graph showing percent MAP4K4 expression in Hek293 cells following lipid mediated transfection of: Guide Strand alone (GS: 8 PS, 19 nt); Guide Strand alone (GS: 18 PS, 19 nt); Nano (GS: no PS, 19 nt); Nano (GS: 2 PS, 19 nt); Nano (GS: 4 PS, 19 nt); Nano (GS: 6 PS, 19 nt); Nano Lead (GS: 8 PS, 19 nt); Nano (GS: 10 PS, 19 nt); Nano (GS: 12 PS, 19 nt); and Nano (GS: 18 PS, 19 nt).

FIG. **41** is a graph showing percent MAP4K4 expression in HeLa cells following passive uptake transfection of: Nano Lead (no Chl); Guide Strand alone (18 PS); Nano (GS: 0 PS, 19 nt); Nano (GS: 2 PS, 19 nt); Nano (GS: 4 PS, 19 nt); Nano (GS: 6 PS, 19 nt); Nano Lead (GS: 8 PS, 19 nt); Nano (GS: 10 PS, 19 nt); Nano (GS: 12 PS, 19 nt); and Nano (GS: 18 PS, 19 nt).

FIG. **42** is a graph showing percent MAP4K4 expression in HeLa cells following passive uptake transfection of: Nano Lead (no Chl); Guide Strand alone (18 PS); Nano (GS: 0 PS, 19 nt); Nano (GS: 2 PS, 19 nt); Nano (GS: 4 PS, 19 nt); Nano (GS: 6 PS, 19 nt); Nano Lead (GS: 8 PS, 19 nt); Nano (GS: 10 PS, 19 nt); Nano (GS: 12 PS, 19 nt); and Nano (GS: 18 PS, 19 nt).

FIG. **43** is a schematic depicting guide strand chemical modifications that were screened for optimization.

FIG. **44** is a graph showing percent MAP4K4 expression in Hek293 cells following reverse transfection of: RISC free siRNA; GS only (2'F C and Us); GS only (2'OMe C and Us); Nano Lead (2'F C and Us); nano (GS: (3) 2'OMe, positions 16-18); nano (GS: (3) 2'OMe, positions 16, 17 and 19); nano (GS: (4) 2'OMe, positions 11, 16-18); nano (GS: (10) 2'OMe, C and Us); nano (GS: (6) 2'OMe, positions 1 and 5-9); nano (GS: (3) 2'OMe, positions 1, 18 and 19); and nano (GS: (5) 2'OMe Cs).

FIG. **45** is a graph demonstrating efficacy of various chemical modification patterns. In particular, 2-OMe modification in positions 1 and 11-18 was well tolerated. 2'OMe modifications in the seed area resulted in a slight reduction of efficacy (but were still highly efficient). Ribo-modifications in the seed were well tolerated. This data enabled the generation of self delivering compounds with reduced or no 2'F modifications. This is significant because 2'F modifications may be associated with toxicity in vivo.

FIG. **46** is a schematic depicting sense strand modifications.

FIG. **47** is a graph demonstrating sense strand length optimization. A sense strand length between 10-15 bases was found to be optimal in this assay. Increasing sense strand length resulted in a reduction of passive uptake of these compounds but may be tolerated for other compounds. Sense strands containing LNA modification demonstrated similar efficacy to non-LNA containing compounds. In some embodiments, the addition of LNA or other thermodynamically stabilizing compounds can be beneficial, resulting in converting non-functional sequences into functional sequences.

FIG. **48** is a graph showing percent MAP4K4 expression in HeLa cells following passive uptake transfection of: Guide Strand Alone (2'F C and U); Nano Lead; Nano Lead (No Chl); Nano (SS: 11 nt 2'OMe C and Us, Chl); Nano (SS: 11 nt, complete 2'OMe, Chl); Nano (SS: 19 nt, 2'OMe C and Us, Chl); Nano (SS: 19 nt, 2'OMe C and Us, no Chl).

FIG. **49** is a graph showing percent MAP4K4 expression in HeLa cells following passive uptake transfection of: Nano Lead (No Chl); Nano (SS no PS); Nano Lead (SS:2 PS); Nano (SS:4 PS).

FIG. **50** is a schematic depicting a sd-rxRNA^{nano} second generation (GII) lead molecule.

FIG. **51** presents a graph indicating EC50 values for MAP4K4 silencing in the presence of sd-rxRNA, and images depicting localization of DY547-labeled rxRNA^{ori} and DY547-labeled sd-rxRNA.

FIG. **52** is a graph showing percent MAP4K4 expression in HeLa cells in the presence of optimized sd-rxRNA molecules.

FIG. **53** is a graph depicting the relevance of chemistry content in optimization of sd-rxRNA efficacy.

FIG. **54** presents schematics of sterol-type molecules and a graph revealing that sd-rxRNA compounds are fully functional with a variety of linker chemistries. GII asymmetric compounds were synthesized with steroltype molecules attached through TEG and amino caproic acid linkers. Both linkers showed identical potency. This functionality independent of linker chemistry indicates a significant difference between the molecules described herein and previously described molecules, and offers significant advantages for the molecules described herein in terms of scale up and synthesis.

FIG. **55** demonstrates the stability of chemically modified sd-rxRNA compounds in human serum in comparison to non modified RNA. The oligonucleotides were incubated in 75% serum at 37° C. for the number of hours indicated. The level of degradation was determined by running the samples on non-denaturing gels and staining with SYBGR.

FIG. **56** is a graph depicting optimization of cellular uptake of sd-rxRNA through minimizing oligonucleotide content.

FIG. **57** is a graph showing percent MAP4K4 expression after spontaneous cellular uptake of sd-rxRNA in mouse

PEC-derived macrophages, and phase and fluorescent images showing localization of sd-rxRNA.

FIG. **58** is a graph showing percent MAP4K4 expression after spontaneous cellular uptake of sd-rxRNA (targeting) and sd-rxRNA (mismatch) in mouse primary hepatocytes, and phase and fluorescent images showing localization of sd-rxRNA.

FIG. **59** presents images depicting localization of DY547-labeled sd-rxRNA delivered to RPE cells with no formulation.

FIG. **60** is a graph showing silencing of MAP4K4 expression in RPE cells treated with sd-rxRNA^{nano} without formulation.

FIG. **61** presents a graph and schematics of RNAi compounds showing the chemical/structural composition of highly effective sd-rxRNA compounds. Highly effective compounds were found to have the following characteristics: antisense strands of 17-21 nucleotides, sense strands of 10-15 nucleotides, single-stranded regions that contained 2-12 phosphorothioate modifications, preferentially 6-8 phosphorothioate modifications, and sense strands in which the majority of nucleotides were 2'OMe modified, with or without phosphorothioate modification. Any linker chemistry can be used to attach these molecules to hydrophobic moieties such as cholesterol at the 3' end of the sense strand. Version GIIa-b of these RNA compounds demonstrate that elimination of 2'F content has no impact on efficacy.

FIG. **62** presents a graph and schematics of RNAi compounds demonstrating the superior performance of sd-rxRNA compounds compared to compounds published by Wolfrum et. al. Nature Biotech, 2007. Both generation I and II compounds (GI and GIIa) developed herein show great efficacy. By contrast, when the chemistry described in Wolfrum et al. (all oligos contain cholesterol conjugated to the 3' end of the sense strand) was applied to the same sequence in a context of conventional siRNA (19 bp duplex with two overhang) the compound was practically inactive. These data emphasize the significance of the combination of chemical modifications and assymetrical molecules described herein, producing highly effective RNA compounds.

FIG. **63** presents images showing that sd-rxRNA accumulates inside cells while other less effective conjugate RNAs accumulate on the surface of cells.

FIG. **64** presents images showing that sd-rxRNA molecules, but not other molecules, are internalized into cells within minutes.

FIG. **65** presents images demonstrating that sd-rxRNA compounds have drastically better cellular and tissue uptake characteristics when compared to conventional cholesterol conjugated siRNAs (such as those published by Soucheck et al). FIG. **65**A,B compare uptake in RPE cells, FIG. **65**C,D compare uptake upon local administration to skin and FIG. **65**E,F compare uptake by the liver upon systemic administration. The level of uptake is at least an order of magnitude higher for the sd-rxRNA compounds relative to the regular siRNA-cholesterol compounds.

FIG. **66** presents images depicting localization of rxRNA^{ori} and sd-rxRNA following local delivery.

FIG. **67** presents images depicting localization of sd-rxRNA and other conjugate RNAs following local delivery.

FIG. **68** presents a graph revealing the results of a screen performed with sd-rxRNAGII chemistry to identify functional compounds targeting the SPP1 gene. Multiple effective compounds were identified, with 14131 being the most effective. The compounds were added to A-549 cells and the level of the ratio of SPP1/PPIB was determined by B-DNA after 48 hours.

FIG. **69** presents a graph and several images demonstrating efficient cellular uptake of sd-rxRNA within minutes of exposure. This is a unique characteristics of the sd-rxRNA compounds described herein, not observed with any other RNAi compounds. The Soutschek et al. compound was used as a negative control.

FIG. **70** presents a graph and several images demonstrating efficient uptake and silencing of sd-rxRNA compounds in multiple cell types with multiple sequences. In each case silencing was confirmed by looking at target gene expression using a Branched DNA assay.

FIG. **71** presents a graph revealing that sd-rxRNA is active in the presence and absence of serum. A slight reduction in efficacy (2-5 fold) was observed in the presence of serum. This minimal reduction in efficacy in the presence of serum differentiates the sd-rxRNA compounds described herein from previously described RNAi compounds, which had a greater reduction in efficacy, and thus creates a foundation for in vivo efficacy of the sd-rxRNA molecules described herein.

FIG. **72** presents images demonstrating efficient tissue penetration and cellular uptake upon single intradermal injection of sd-rxRNA compounds described herein. This represents a model for local delivery of sd-rxRNA compounds as well as an effective demonstration of delivery of sd-rxRNA compounds and silencing of genes in dermatological applications.

FIG. **73** presents images and a graph demonstrating efficient cellular uptake and in vivo silencing with sd-rxRNA following intradermal injection.

FIG. **74** presents graphs demonstrating that sd-rxRNA compounds have improved blood clearance and induce effective gene silencing in vivo in the liver upon systemic administration.

FIG. **75** presents a graph demonstrating that the presence of 5-Methyl C in an RNAi compound resulted in an increase in potency of lipid mediated transfection, demonstrating that hydrophobic modification of Cs and Us in the content of RNAi compounds can be beneficial. In some embodiments, these types of modifications can be used in the context of 2' ribose modified bases to insure optimal stability and efficacy.

FIG. **76** presents a graph showing percent MAP4K4 expression in HeLa cells following passive uptake transfection of: Guide strand alone; Nano Lead; Nano Lead (No cholesterol); Guide Strand w/SMeC and 2'F Us Alone; Nano Lead w/GS SMeC and 2'F Us; Nano Lead w/GS riboT and 5 Methyl Cs; and Nano Lead w/Guide dT and 5 Methyl Cs.

FIG. **77** presents images comparing localization of sd-rxRNA and other RNA conjugates following systemic delivery to the liver.

FIG. **78** presents schematics demonstrating 5-uridyl modifications with improved hydrophobicity characteristics. Incorporation of such modifications into sd-rxRNA compounds can increase cellular and tissue uptake properties. FIG. **78**B presents a new type of RNAi compound modification which can be applied to compounds to improve cellular uptake and pharmacokinetic behavior. This type of modification, when applied to sd-rxRNA compounds, may contribute to making such compounds orally available.

FIG. **79** presents schematics revealing the structures of synthesized modified sterol type molecules, where the length and structure of the C17 attached tail is modified. Without wishing to be bound by any theory, the length of the C17 attached tail may contribute to improving in vitro and in vivo efficacy of sd-rxRNA compounds.

FIG. **80** presents a schematic demonstrating the lithocholic acid route to long side chain cholesterols.

FIG. **81** presents a schematic demonstrating a route to 5-uridyl phosphoramidite synthesis.

FIG. **82** presents a schematic demonstrating synthesis of tri-functional hydroxyprolinol linker for 3'-cholesterol attachment.

FIG. **83** presents a schematic demonstrating synthesis of solid support for the manufacture of a shorter asymmetric RNAi compound strand.

FIG. **84** demonstrates SPPI sd-rxRNA compound selection. Sd-rxRNA compounds targeting SPP1 were added to A549 cells (using passive transfection) and the level of SPP1 expression was evaluated after 48 hours. Several novel compounds effective in SPP1 silencing were identified, the most potent of which was compound 14131.

FIG. **85** demonstrates independent validation of sd-rxRNA compounds 14116, 14121, 14131, 14134, 14139, 14149, and 14152 efficacy in SPP1 silencing.

FIG. **86** demonstrates results of sd-rxRNA compound screens to identify sd-rxRNA compounds functional in CTGF knockdown.

FIG. **87** demonstrates results of sd-rxRNA compound screens to identify sd-rxRNA functional in CTGF knockdown.

FIG. **88** demonstrates a systematic screen identifying the minimal length of the asymmetric compounds. The passenger strand of 10-19 bases was hybridized to a guide strand of 17-25 bases. In this assay, compounds with duplex regions as short as 10 bases were found to be effective in inducing.

FIG. **89** demonstrates that positioning of the sense strand relative to the guide strand is critical for RNAi Activity. In this assay, a blunt end was found to be optimal, a 3' overhang was tolerated, and a 5' overhang resulted in complete loss of functionality.

FIG. **90** demonstrates that the guide strand, which has homology to the target only at nucleotides 2-17, resulted in effective RNAi when hybridized with sense strands of different lengths. The compounds were introduced into HeLa cells via lipid mediated transfection.

FIG. **91** is a schematic depicting a panel of sterol-type molecules which can be used as a hydrophobic entity in place of cholesterol. In some instances, the use of sterol-type molecules comprising longer chains results in generation of sd-rxRNA compounds with significantly better cellular uptake and tissue distribution properties.

FIG. **92** presents schematics depicting a panel of hydrophobic molecules which might be used as a hydrophobic entity in place of cholesterol. These list just provides representative examples; any small molecule with substantial hydrophobicity can be used.

DETAILED DESCRIPTION

Aspects of the invention relate to methods and compositions involved in gene silencing. The invention is based at least in part on the surprising discovery that asymmetric nucleic acid molecules with a double stranded region of a minimal length such as 8-14 nucleotides, are effective in silencing gene expression. Molecules with such a short double stranded region have not previously been demonstrated to be effective in mediating RNA interference. It had previously been assumed that that there must be a double stranded region of 19 nucleotides or greater. The molecules described herein are optimized through chemical modification, and in some instances through attachment of hydrophobic conjugates.

The invention is based at least in part on another surprising discovery that asymmetric nucleic acid molecules with reduced double stranded regions are much more effectively taken up by cells compared to conventional siRNAs. These molecules are highly efficient in silencing of target gene expression and offer significant advantages over previously described RNAi molecules including high activity in the presence of serum, efficient self delivery, compatibility with a wide variety of linkers, and reduced presence or complete absence of chemical modifications that are associated with toxicity.

In contrast to single-stranded polynucleotides, duplex polynucleotides have been difficult to deliver to a cell as they have rigid structures and a large number of negative charges which makes membrane transfer difficult. Unexpectedly, it was found that the polynucleotides of the present invention, although partially double-stranded, are recognized in vivo as single-stranded and, as such, are capable of efficiently being delivered across cell membranes. As a result the polynucleotides of the invention are capable in many instances of self delivery. Thus, the polynucleotides of the invention may be formulated in a manner similar to conventional RNAi agents or they may be delivered to the cell or subject alone (or with non-delivery type carriers) and allowed to self deliver. In one embodiment of the present invention, self delivering asymmetric double-stranded RNA molecules are provided in which one portion of the molecule resembles a conventional RNA duplex and a second portion of the molecule is single stranded.

The polynucleotides of the invention are referred to herein as isolated double stranded or duplex nucleic acids, oligonucleotides or polynucleotides, nano molecules, nano RNA, sd-rxRNA^{nano}, sd-rxRNA or RNA molecules of the invention.

The oligonucleotides of the invention in some aspects have a combination of asymmetric structures including a double stranded region and a single stranded region of 5 nucleotides or longer, specific chemical modification patterns and are conjugated to lipophilic or hydrophobic molecules. This new class of RNAi like compounds have superior efficacy in vitro and in vivo. Based on the data described herein it is believed that the reduction in the size of the rigid duplex region in combination with phosphorothioate modifications applied to a single stranded region are new and important for achieving the observed superior efficacy. Thus, the RNA molecules described herein are different in both structure and composition as well as in vitro and in vivo activity.

In a preferred embodiment the RNAi compounds of the invention comprise an asymmetric compound comprising a duplex region (required for efficient RISC entry of 10-15 bases long) and single stranded region of 4-12 nucleotides long; with a 13 nucleotide duplex. A 6 nucleotide single stranded region is preferred in some embodiments. The single stranded region of the new RNAi compounds also comprises 2-12 phosphorothioate internucleotide linkages (referred to as phosphorothioate modifications). 6-8 phosphorothioate internucleotide linkages are preferred in some embodiments. Additionally, the RNAi compounds of the invention also include a unique chemical modification pattern, which provides stability and is compatible with RISC entry. The combination of these elements has resulted in unexpected properties which are highly useful for delivery of RNAi reagents in vitro and in vivo.

The chemically modification pattern, which provides stability and is compatible with RISC entry includes modifications to the sense, or passenger, strand as well as the antisense, or guide, strand. For instance the passenger strand can be modified with any chemical entities which confirm stability and do not interfere with activity. Such modifications include 2' ribo modifications (O-methyl, 2' F, 2 deoxy and others) and backbone modification like phosphorothioate modifications. A preferred chemical modification pattern in the passenger strand includes Omethyl modification of C and U nucleotides within the passenger strand or alternatively the passenger strand may be completely Omethyl modified.

The guide strand, for example, may also be modified by any chemical modification which confirms stability without interfering with RISC entry. A preferred chemical modification pattern in the guide strand includes the majority of C and U nucleotides being 2' F modified and the 5' end being phosphorylated. Another preferred chemical modification pattern in the guide strand includes 2' Omethyl modification of position 1 and C/U in positions 11-18 and 5' end chemical phosphorylation. Yet another preferred chemical modification pattern in the guide strand includes 2' Omethyl modification of position 1 and C/U in positions 11-18 and 5' end chemical phosphorylation and 2'F modification of C/U in positions 2-10.

It was surprisingly discovered according to the invention that the above-described chemical modification patterns of the oligonucleotides of the invention are well tolerated and actually improved efficacy of asymmetric RNAi compounds. See, for instance, FIG. **22**.

It was also demonstrated experimentally herein that the combination of modifications to RNAi when used together in a polynucleotide results in the achievement of optimal efficacy in passive uptake of the RNAi. Elimination of any of the described components (Guide strand stabilization, phosphorothioate stretch, sense strand stabilization and hydrophobic conjugate) or increase in size results in sub-optimal efficacy and in some instances complete lost of efficacy. The combination of elements results in development of compound, which is fully active following passive delivery to cells such as HeLa cells. (FIG. **23**). The degree to which the combination of elements results in efficient self delivery of RNAi molecules was completely unexpected.

The data shown in FIGS. **26**, **27** and **43** demonstrated the importance of the various modifications to the RNAi in achieving stabilization and activity. For instance, FIG. **26** demonstrates that use off asymmetric configuration is important in getting efficacy in passive uptake. When the same chemical composition is applied to compounds of traditional configurations (19-21 bases duplex and 25 mer duplex) the efficacy was drastically decreased in a length dependent manner. FIG. **27** demonstrated a systematic screen of the impact of phosphorothioate chemical modifications on activity. The sequence, structure, stabilization chemical modifications, hydrophobic conjugate were kept constant and compound phosphorothioate content was varied (from 0 to 18 PS bond). Both compounds having no phosphorothioate linkages and having 18 phosphorothioate linkages were completely inactive in passive uptake. Compounds having 2-16 phosphorothioate linkages were active, with compounds having 4-10 phosphorothioate being the most active compounds.

The data in the Examples presented below demonstrates high efficacy of the oligonucleotides of the invention both in vitro in variety of cell types (supporting data) and in vivo upon local and systemic administration. For instance, the data compares the ability of several competitive RNAi molecules having different chemistries to silence a gene. Comparison of sd-rxRNA (oligonucleotides of the invention) with RNAs described in Soucheck et al. and Wolfrum at al., as applied to the same targeting region, demonstrated that only sd-rxRNA chemistry showed a significant functionality in passive uptake. The composition of the invention achieved EC50 values of 10-50 μM. This level of efficacy is un-attainable with conventional chemistries like those described in Sauthceck at al and Accell. Similar comparisons were made in other systems, such as in vitro (RPE cell line), in vivo upon local administration (wounded skin) and systemic (50 mg/kg) as well as other genes (FIGS. **65** and **68**). In each case the oligonucleotides of the invention achieved better results. FIG. **64** includes data demonstrating efficient cellular uptake and resulting silencing by sd-rxRNA compounds only after 1 minute of exposure. Such an efficacy is unique to this composition and have not been seen with other types of molecules in this class. FIG. **70** demonstrates efficient uptake and silencing of sd-rxRNA compounds in multiple cell types with multiple sequences. The sd-rxRNA compounds are also active in cells in presence and absence of serum and other biological liquids. FIG. **71** demonstrates only a slight reduction in activity in the presence of serum. This ability to function in biologically aggressive environment effectively further differentiates sd-rxRNA compounds from other compounds described previously in this group, like Accell and Soucheck et al, in which uptake is drastically inhibited in a presence of serum.

Significant amounts of data also demonstrate the in vivo efficacy of the compounds of the invention. For instance FIGS. **72-74** involve multiple routes of in vivo delivery of the compounds of the invention resulting in significant activity. FIG. **72**, for example, demonstrates efficient tissue penetration and cellular uptake upon single intradermal injection. This is a model for local delivery of sd-rxRNA compounds as well as an effective delivery mode for sd-rxRNA compounds and silencing genes in any dermatology applications. FIG. **73** demonstrated efficient tissue penetration, cellular uptake and silencing upon local in vivo intradermal injection of sd-rxRNA compounds. The data of FIG. **74** demonstrate that sd-rxRNA compounds result in highly effective liver uptake upon IV administration. Comparison to Souicheck at al molecule showed that the level of liver uptake at identical dose level was quite surprisingly, at least 50 fold higher with the sd-rxRNA compound than the Souicheck at al molecule.

The sd-rxRNA can be further improved in some instances by improving the hydrophobicity of compounds using of novel types of chemistries. For example one chemistry is related to use of hydrophobic base modifications. Any base in any position might be modified, as long as modification results in an increase of the partition coefficient of the base. The preferred locations for modification chemistries are positions 4 and 5 of the pyrimidines. The major advantage of these positions is (a) ease of synthesis and (b) lack of interference with base-pairing and A form helix formation, which are essential for RISC complex loading and target recognition. Examples of these chemistries is shown in FIGS. **75-83**. A version of sd-rxRNA compounds where multiple deoxy Uridines are present without interfering with overall compound efficacy was used. In addition major improvement in tissue distribution and cellular uptake might be obtained by optimizing the structure of the hydrophobic conjugate. In some of the preferred embodiment the structure of sterol is modified to alter (increase/decrease) C17 attached chain. This type of modification results in significant increase in cellular uptake and improvement of tissue uptake prosperities in vivo.

This invention is not limited in its application to the details of construction and the arrangement of components set forth in the following description or illustrated in the drawings. The invention is capable of other embodiments and of being practiced or of being carried out in various ways. Also, the phraseology and terminology used herein is for the purpose of description and should not be regarded as limiting. The use of "including," "comprising," or "having," "containing," "involving," and variations thereof herein, is meant to encompass the items listed thereafter and equivalents thereof as well as additional items.

Thus, aspects of the invention relate to isolated double stranded nucleic acid molecules comprising a guide (antisense) strand and a passenger (sense) strand. As used herein, the term "double-stranded" refers to one or more nucleic acid molecules in which at least a portion of the nucleomonomers are complementary and hydrogen bond to form a double-stranded region. In some embodiments, the length of the guide strand ranges from 16-29 nucleotides long. In certain embodiments, the guide strand is 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, or 29 nucleotides long. The guide strand has complementarity to a target gene. Complementarity between the guide strand and the target gene may exist over any portion of the guide strand. Complementarity as used herein may be perfect complementarity or less than perfect complementarity as long as the guide strand is sufficiently complementary to the target that it mediates RNAi. In some embodiments complementarity refers to less than 25%, 20%, 15%, 10%, 5%, 4%, 3%, 2%, or 1% mismatch between the guide strand and the target. Perfect complementarity refers to 100% complementarity. Thus the invention has the advantage of being able to tolerate sequence variations that might be expected due to genetic mutation, strain polymorphism, or evolutionary divergence. For example, siRNA sequences with insertions, deletions, and single point mutations relative to the target sequence have also been found to be effective for inhibition. Moreover, not all positions of a siRNA contribute equally to target recognition. Mismatches in the center of the siRNA are most critical and essentially abolish target RNA cleavage. Mismatches upstream of the center or upstream of the cleavage site referencing the antisense strand are tolerated but significantly reduce target RNA cleavage. Mismatches downstream of the center or cleavage site referencing the antisense strand, preferably located near the 3' end of the antisense strand, e.g. 1, 2, 3, 4, 5 or 6 nucleotides from the 3' end of the antisense strand, are tolerated and reduce target RNA cleavage only slightly.

While not wishing to be bound by any particular theory, in some embodiments, the guide strand is at least 16 nucleotides in length and anchors the Argonaute protein in RISC. In some embodiments, when the guide strand loads into RISC it has a defined seed region and target mRNA cleavage takes place across from position 10-11 of the guide strand. In some embodiments, the 5' end of the guide strand is or is able to be phosphorylated. The nucleic acid molecules described herein may be referred to as minimum trigger RNA.

In some embodiments, the length of the passenger strand ranges from 8-14 nucleotides long. In certain embodiments, the passenger strand is 8, 9, 10, 11, 12, 13 or 14 nucleotides long. The passenger strand has complementarity to the guide strand. Complementarity between the passenger strand and the guide strand can exist over any portion of the passenger or guide strand. In some embodiments, there is 100% complementarity between the guide and passenger strands within the double stranded region of the molecule.

Aspects of the invention relate to double stranded nucleic acid molecules with minimal double stranded regions. In some embodiments the region of the molecule that is double stranded ranges from 8-14 nucleotides long. In certain embodiments, the region of the molecule that is double stranded is 8, 9, 10, 11, 12, 13 or 14 nucleotides long. In certain embodiments the double stranded region is 13 nucleotides long. There can be 100% complementarity between the guide and passenger strands, or there may be one or more mismatches between the guide and passenger strands. In some embodiments, on one end of the double stranded molecule, the molecule is either blunt-ended or has a one-nucleotide overhang. The single stranded region of the molecule is in some embodiments between 4-12 nucleotides long. For example the single stranded region can be 4, 5, 6, 7, 8, 9, 10, 11 or 12 nucleotides long. However, in certain embodiments, the single stranded region can also be less than 4 or greater than 12 nucleotides long. In certain embodiments, the single stranded region is 6 nucleotides long.

RNAi constructs associated with the invention can have a thermodynamic stability (AG) of less than −13 kkal/mol. In some embodiments, the thermodynamic stability (AG) is less than −20 kkal/mol. In some embodiments there is a loss of efficacy when (AG) goes below −21 kkal/mol. In some embodiments a (ΔG) value higher than −13 kkal/mol is compatible with aspects of the invention. Without wishing to be bound by any theory, in some embodiments a molecule with a relatively higher (ΔG) value may become active at a relatively higher concentration, while a molecule with a relatively lower (ΔG) value may become active at a relatively lower concentration. In some embodiments, the (ΔG) value may be higher than −9 kkcal/mol. The gene silencing effects mediated by the RNAi constructs associated with the invention, containing minimal double stranded regions, are unexpected because molecules of almost identical design but lower thermodynamic stability have been demonstrated to be inactive (Rana et al 2004).

Without wishing to be bound by any theory, results described herein suggest that a stretch of 8-10 bp of dsRNA or dsDNA will be structurally recognized by protein components of RISC or co-factors of RISC. Additionally, there is a free energy requirement for the triggering compound that it may be either sensed by the protein components and/or stable enough to interact with such components so that it may be loaded into the Argonaute protein. If optimal thermodynamics are present and there is a double stranded portion that is preferably at least 8 nucleotides then the duplex will be recognized and loaded into the RNAi machinery.

In some embodiments, thermodynamic stability is increased through the use of LNA bases. In some embodiments, additional chemical modifications are introduced. Several non-limiting examples of chemical modifications include: 5' Phosphate, 2'-O-methyl, 2'-O-ethyl, 2'-fluoro, ribothymidine, C-5 propynyl-dC (pdC) and C-5 propynyl-dU (pdU); C-5 propynyl-C (pC) and C-5 propynyl-U (pU); 5-methyl C, 5-methyl U, 5-methyl dC, 5-methyl dU methoxy, (2,6-diaminopurine), 5'-Dimethoxytrityl-N4-ethyl-2'-deoxy-Cytidine and MGB (minor groove binder). It should be appreciated that more than one chemical modification can be combined within the same molecule.

Molecules associated with the invention are optimized for increased potency and/or reduced toxicity. For example, nucleotide length of the guide and/or passenger strand, and/or the number of phosphorothioate modifications in the guide and/or passenger strand, can in some aspects influence potency of the RNA molecule, while replacing 2'-fluoro (2'F) modifications with 2'-O-methyl (2'OMe) modifications can in some aspects influence toxicity of the molecule. Specifically, reduction in 2'F content of a molecule is predicted to reduce toxicity of the molecule. The Examples section presents molecules in which 2'F modifications have been eliminated, offering an advantage over previously described RNAi compounds due to a predicted reduction in toxicity. Furthermore, the number of phosphorothioate modifications in an RNA molecule can influence the uptake of the molecule into a cell, for example the efficiency of passive uptake of the molecule into a cell. Preferred embodiments of molecules described herein have no 2'F modification and yet are characterized by equal efficacy in cellular uptake and tissue penetration. Such molecules represent a significant improvement over prior art, such as molecules described by Accell and Wolfrum, which are heavily modified with extensive use of 2'F.

In some embodiments, a guide strand is approximately 18-19 nucleotides in length and has approximately 2-14 phosphate modifications. For example, a guide strand can contain 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14 or more than 14 nucleotides that are phosphate-modified. The guide strand may contain one or more modifications that confer increased stability without interfering with RISC entry. The phosphate modified nucleotides, such as phosphorothioate modified nucleotides, can be at the 3' end, 5' end or spread throughout the guide strand. In some embodiments, the 3' terminal 10 nucleotides of the guide strand contains 1, 2, 3, 4, 5, 6, 7, 8, 9 or 10 phosphorothioate modified nucleotides. The guide strand can also contain 2'F and/or 2'OMe modifications, which can be located throughout the molecule. In some embodiments, the nucleotide in position one of the guide strand (the nucleotide in the most 5' position of the guide strand) is 2'OMe modified and/or phosphorylated. C and U nucleotides within the guide strand can be 2'F modified. For example, C and U nucleotides in positions 2-10 of a 19 nt guide strand (or corresponding positions in a guide strand of a different length) can be 2'F modified. C and U nucleotides within the guide strand can also be 2'OMe modified. For example, C and U nucleotides in positions 11-18 of a 19 nt guide strand (or corresponding positions in a guide strand of a different length) can be 2'OMe modified. In some embodiments, the nucleotide at the most 3' end of the guide strand is unmodified. In certain embodiments, the majority of Cs and Us within the guide strand are 2'F modified and the 5' end of the guide strand is phosphorylated. In other embodiments, position 1 and the Cs or Us in positions 11-18 are 2'OMe modified and the 5' end of the guide strand is phosphorylated. In other embodiments, position 1 and the Cs or Us in positions 11-18 are 2'OMe modified, the 5' end of the guide strand is phosphorylated, and the Cs or Us in position 2-10 are 2'F modified.

In some aspects, an optimal passenger strand is approximately 11-14 nucleotides in length. The passenger strand may contain modifications that confer increased stability. One or more nucleotides in the passenger strand can be 2'OMe modified. In some embodiments, one or more of the C and/or U nucleotides in the passenger strand is 2'OMe modified, or all of the C and U nucleotides in the passenger strand are 2'OMe modified. In certain embodiments, all of the nucleotides in the passenger strand are 2'OMe modified. One or more of the nucleotides on the passenger strand can also be phosphate-modified such as phosphorothioate modified. The passenger strand can also contain 2' ribo, 2'F and 2 deoxy modifications or any combination of the above. As demonstrated in the Examples, chemical modification patterns on both the guide and passenger strand are well tolerated and a combination of chemical modifications is shown herein to lead to increased efficacy and self-delivery of RNA molecules.

Aspects of the invention relate to RNAi constructs that have extended single-stranded regions relative to double stranded regions, as compared to molecules that have been used previously for RNAi. The single stranded region of the molecules may be modified to promote cellular uptake or gene silencing. In some embodiments, phosphorothioate modification of the single stranded region influences cellular uptake and/or gene silencing. The region of the guide strand that is phosphorothioate modified can include nucleotides within both the single stranded and double stranded regions of the molecule. In some embodiments, the single stranded region includes 2-12 phosphorothioate modifications. For example, the single stranded region can include 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, or 12 phosphorothioate modifications. In some instances, the single stranded region contains 6-8 phosphorothioate modifications.

Molecules associated with the invention are also optimized for cellular uptake. In RNA molecules described herein, the guide and/or passenger strands can be attached to a conjugate. In certain embodiments the conjugate is hydrophobic. The hydrophobic conjugate can be a small molecule with a partition coefficient that is higher than 10. The conjugate can be a sterol-type molecule such as cholesterol, or a molecule with an increased length polycarbon chain attached to C17, and the presence of a conjugate can influence the ability of an RNA molecule to be taken into a cell with or without a lipid transfection reagent. The conjugate can be attached to the passenger or guide strand through a hydrophobic linker. In some embodiments, a hydrophobic linker is 5-12C in length, and/or is hydroxypyrrolidine-based. In some embodiments, a hydrophobic conjugate is attached to the passenger strand and the CU residues of either the passenger and/or guide strand are modified. In some embodiments, at least 50%, 55%, 60%, 65%, 70%, 75%, 80%, 85%, 90% or 95% of the CU residues on the passenger strand and/or the guide strand are modified. In some aspects, molecules associated with the invention are self-delivering (sd). As used herein, “self-delivery” refers to the ability of a molecule to be delivered into a cell without the need for an additional delivery vehicle such as a transfection reagent.

Aspects of the invention relate to selecting molecules for use in RNAi. Based on the data described herein, molecules that have a double stranded region of 8-14 nucleotides can be selected for use in RNAi. In some embodiments, molecules are selected based on their thermodynamic stability (ΔG). In some embodiments, molecules will be selected that have a (AG) of less than −13 kkal/mol. For example, the (ΔG) value may be −13, −14, −15, −16, −17, −18, −19, −21, −22 or less than −22 kkal/mol. In other embodiments, the (ΔG) value may be higher than −13 kkal/mol. For example, the (AG) value may be −12, −11, −10, −9, −8, −7 or more than −7 kkal/mol. It should be appreciated that ΔG can be calculated using any method known in the art. In some embodiments ΔG is calculated using Mfold, available through the Mfold internet site (http://mfold.bioinfo.rpi.edu/cgi-bin/rna-form1.cgi). Methods for calculating ΔG are described in, and are incorporated by reference from, the following references: Zuker, M. (2003) Nucleic Acids Res., 31(13):3406-15; Mathews, D. H., Sabina, J., Zuker, M. and Turner, D. H. (1999) J. Mol. Biol. 288:911-940; Mathews, D. H., Disney, M. D., Childs, J. L., Schroeder, S. J., Zuker, M., and Turner, D. H. (2004) Proc. Natl. Acad. Sci. 101:7287-7292; Duan, S., Mathews, D. H., and Turner, D. H. (2006) Biochemistry 45:9819-9832; Wuchty, S., Fontana, W., Hofacker, I. L., and Schuster, P. (1999) Biopolymers 49:145-165.

Aspects of the invention relate to using nucleic acid molecules described herein, with minimal double stranded regions and/or with a (ΔG) of less than −13 kkal/mol, for gene silencing. RNAi molecules can be administered in vivo or in vitro, and gene silencing effects can be achieved in vivo or in vitro.

In certain embodiments, the polynucleotide contains 5'- and/or 3'-end overhangs. The number and/or sequence of nucleotides overhang on one end of the polynucleotide may be the same or different from the other end of the polynucleotide. In certain embodiments, one or more of the overhang nucleotides may contain chemical modification(s), such as phosphorothioate or 2'-OMe modification.

In certain embodiments, the polynucleotide is unmodified. In other embodiments, at least one nucleotide is modified. In further embodiments, the modification includes a 2'-H or 2'-modified ribose sugar at the 2nd nucleotide from the 5'-end of the guide sequence. The "2nd nucleotide" is defined as the second nucleotide from the 5'-end of the polynucleotide.

As used herein, "2'-modified ribose sugar" includes those ribose sugars that do not have a 2'-OH group. "2'-modified ribose sugar" does not include 2'-deoxyribose (found in unmodified canonical DNA nucleotides). For example, the 2'-modified ribose sugar may be 2'-O-alkyl nucleotides, 2'-deoxy-2'-fluoro nucleotides, 2'-deoxy nucleotides, or combination thereof.

In certain embodiments, the 2'-modified nucleotides are pyrimidine nucleotides (e.g., C/U). Examples of 2'-O-alkyl nucleotides include 2'-O-methyl nucleotides, or 2'-O-allyl nucleotides.

In certain embodiments, the miniRNA polynucleotide of the invention with the above-referenced 5'-end modification exhibits significantly (e.g., at least about 25%, 30%, 35%, 40%, 45%, 50%, 55%, 60%, 65%, 70%, 75%, 80%, 85%, 90% or more) less "off-target" gene silencing when compared to similar constructs without the specified 5'-end modification, thus greatly improving the overall specificity of the RNAi reagent or therapeutics.

As used herein, "off-target" gene silencing refers to unintended gene silencing due to, for example, spurious sequence homology between the antisense (guide) sequence and the unintended target mRNA sequence.

According to this aspect of the invention, certain guide strand modifications further increase nuclease stability, and/or lower interferon induction, without significantly decreasing RNAi activity (or no decrease in RNAi activity at all).

In some embodiments, the 5'-stem sequence may comprise a 2'-modified ribose sugar, such as 2'-O-methyl modified nucleotide, at the 2^{nd} nucleotide on the 5'-end of the polynucleotide and, in some embodiments, no other modified nucleotides. The hairpin structure having such modification may have enhanced target specificity or reduced off-target silencing compared to a similar construct without the 2'-O-methyl modification at said position.

Certain combinations of specific 5'-stem sequence and 3'-stem sequence modifications may result in further unexpected advantages, as partly manifested by enhanced ability to inhibit target gene expression, enhanced serum stability, and/or increased target specificity, etc.

In certain embodiments, the guide strand comprises a 2'-O-methyl modified nucleotide at the 2^{nd} nucleotide on the 5'-end of the guide strand and no other modified nucleotides.

In other aspects, the miniRNA structures of the present invention mediates sequence-dependent gene silencing by a microRNA mechanism. As used herein, the term "microRNA" ("miRNA"), also referred to in the art as "small temporal RNAs" ("stRNAs"), refers to a small (10-50 nucleotide) RNA which are genetically encoded (e.g., by viral, mammalian, or plant genomes) and are capable of directing or mediating RNA silencing. An "miRNA disorder" shall refer to a disease or disorder characterized by an aberrant expression or activity of an miRNA.

microRNAs are involved in down-regulating target genes in critical pathways, such as development and cancer, in mice, worms and mammals. Gene silencing through a microRNA mechanism is achieved by specific yet imperfect base-pairing of the miRNA and its target messenger RNA (mRNA). Various mechanisms may be used in microRNA-mediated down-regulation of target mRNA expression.

miRNAs are noncoding RNAs of approximately 22 nucleotides which can regulate gene expression at the post transcriptional or translational level during plant and animal development. One common feature of miRNAs is that they are all excised from an approximately 70 nucleotide precursor RNA stem-loop termed pre-miRNA, probably by Dicer, an RNase III-type enzyme, or a homolog thereof. Naturally-occurring miRNAs are expressed by endogenous genes in vivo and are processed from a hairpin or stem-loop precursor (pre-miRNA or pri-miRNAs) by Dicer or other RNAses. miRNAs can exist transiently in vivo as a double-stranded duplex but only one strand is taken up by the RISC complex to direct gene silencing.

In some embodiments a version of sd-rxRNA compounds, which are effective in cellular uptake and inhibiting of miRNA activity are described. Essentially the compounds are similar to RISC entering version but large strand chemical modification patterns are optimized in the way to block cleavage and act as an effective inhibitor of the RISC action. For example, the compound might be completely or mostly Omethyl modified with the PS content described previously. For these types of compounds the 5' phosphorilation is not necessary. The presence of double stranded region is preferred as it is promotes cellular uptake and efficient RISC loading.

Another pathway that uses small RNAs as sequence-specific regulators is the RNA interference (RNAi) pathway, which is an evolutionarily conserved response to the presence of double-stranded RNA (dsRNA) in the cell. The dsRNAs are cleaved into ~20-base pair (bp) duplexes of small-interfering RNAs (siRNAs) by Dicer. These small RNAs get assembled into multiprotein effector complexes called RNA-induced silencing complexes (RISCs). The siRNAs then guide the cleavage of target mRNAs with perfect complementarity.

Some aspects of biogenesis, protein complexes, and function are shared between the siRNA pathway and the miRNA pathway. The subject single-stranded polynucleotides may mimic the dsRNA in the siRNA mechanism, or the microRNA in the miRNA mechanism.

In certain embodiments, the modified RNAi constructs may have improved stability in serum and/or cerebral spinal fluid compared to an unmodified RNAi constructs having the same sequence.

In certain embodiments, the structure of the RNAi construct does not induce interferon response in primary cells, such as mammalian primary cells, including primary cells from human, mouse and other rodents, and other non-human mammals. In certain embodiments, the RNAi construct may also be used to inhibit expression of a target gene in an invertebrate organism.

To further increase the stability of the subject constructs in vivo, the 3'-end of the hairpin structure may be blocked by protective group(s). For example, protective groups such as inverted nucleotides, inverted abasic moieties, or amino-end modified nucleotides may be used. Inverted nucleotides may comprise an inverted deoxynucleotide. Inverted abasic moieties may comprise an inverted deoxyabasic moiety, such as a 3',3'-linked or 5',5'-linked deoxyabasic moiety.

The RNAi constructs of the invention are capable of inhibiting the synthesis of any target protein encoded by target gene(s). The invention includes methods to inhibit expression of a target gene either in a cell in vitro, or in vivo. As such, the

RNAi constructs of the invention are useful for treating a patient with a disease characterized by the overexpression of a target gene.

The target gene can be endogenous or exogenous (e.g., introduced into a cell by a virus or using recombinant DNA technology) to a cell. Such methods may include introduction of RNA into a cell in an amount sufficient to inhibit expression of the target gene. By way of example, such an RNA molecule may have a guide strand that is complementary to the nucleotide sequence of the target gene, such that the composition inhibits expression of the target gene.

The invention also relates to vectors expressing the nucleic acids of the invention, and cells comprising such vectors or the nucleic acids. The cell may be a mammalian cell in vivo or in culture, such as a human cell.

The invention further relates to compositions comprising the subject RNAi constructs, and a pharmaceutically acceptable carrier or diluent.

Another aspect of the invention provides a method for inhibiting the expression of a target gene in a mammalian cell, comprising contacting the mammalian cell with any of the subject RNAi constructs.

The method may be carried out in vitro, ex vivo, or in vivo, in, for example, mammalian cells in culture, such as a human cell in culture.

The target cells (e.g., mammalian cell) may be contacted in the presence of a delivery reagent, such as a lipid (e.g., a cationic lipid) or a liposome.

Another aspect of the invention provides a method for inhibiting the expression of a target gene in a mammalian cell, comprising contacting the mammalian cell with a vector expressing the subject RNAi constructs.

In one aspect of the invention, a longer duplex polynucleotide is provided, including a first polynucleotide that ranges in size from about 16 to about 30 nucleotides; a second polynucleotide that ranges in size from about 26 to about 46 nucleotides, wherein the first polynucleotide (the antisense strand) is complementary to both the second polynucleotide (the sense strand) and a target gene, and wherein both polynucleotides form a duplex and wherein the first polynucleotide contains a single stranded region longer than 6 bases in length and is modified with alternative chemical modification pattern, and/or includes a conjugate moiety that facilitates cellular delivery. In this embodiment, between about 40% to about 90% of the nucleotides of the passenger strand between about 40% to about 90% of the nucleotides of the guide strand, and between about 40% to about 90% of the nucleotides of the single stranded region of the first polynucleotide are chemically modified nucleotides.

In an embodiment, the chemically modified nucleotide in the polynucleotide duplex may be any chemically modified nucleotide known in the art, such as those discussed in detail above. In a particular embodiment, the chemically modified nucleotide is selected from the group consisting of 2' F modified nucleotides, 2'-β-methyl modified and 2' deoxy nucleotides. In another particular embodiment, the chemically modified nucleotides results from "hydrophobic modifications" of the nucleotide base. In another particular embodiment, the chemically modified nucleotides are phosphorothioates. In an additional particular embodiment, chemically modified nucleotides are combination of phosphorothioates, 2'-O-methyl, 2' deoxy, hydrophobic modifications and phosphorothioates. As these groups of modifications refer to modification of the ribose ring, back bone and nucleotide, it is feasible that some modified nucleotides will carry a combination of all three modification types.

In another embodiment, the chemical modification is not the same across the various regions of the duplex. In a particular embodiment, the first polynucleotide (the passenger strand), has a large number of diverse chemical modifications in various positions. For this polynucleotide up to 90% of nucleotides might be chemically modified and/or have mismatches introduced.

In another embodiment, chemical modifications of the first or second polynucleotide include, but not limited to, 5' position modification of Uridine and Cytosine (4-pyridyl, 2-pyridyl, indolyl, phenyl (C_6H_5OH); tryptophanyl (C8H6N) CH2CH(NH2)CO), isobutyl, butyl, aminobenzyl; phenyl; naphthyl, etc), where the chemical modification might alter base pairing capabilities of a nucleotide. For the guide strand an important feature of this aspect of the invention is the position of the chemical modification relative to the 5' end of the antisense and sequence. For example, chemical phosphorylation of the 5' end of the guide strand is usually beneficial for efficacy. O-methyl modifications in the seed region of the sense strand (position 2-7 relative to the 5' end) are not generally well tolerated, whereas 2'F and deoxy are well tolerated. The mid part of the guide strand and the 3' end of the guide strand are more permissive in a type of chemical modifications applied. Deoxy modifications are not tolerated at the 3' end of the guide strand.

A unique feature of this aspect of the invention involves the use of hydrophobic modification on the bases. In one embodiment, the hydrophobic modifications are preferably positioned near the 5' end of the guide strand, in other embodiments, they localized in the middle of the guides strand, in other embodiment they localized at the 3' end of the guide strand and yet in another embodiment they are distributed thought the whole length of the polynucleotide. The same type of patterns is applicable to the passenger strand of the duplex.

The other part of the molecule is a single stranded region. The single stranded region is expected to range from 7 to 40 nucleotides.

In one embodiment, the single stranded region of the first polynucleotide contains modifications selected from the group consisting of between 40% and 90% hydrophobic base modifications, between 40%-90% phosphorothioates, between 40%-90% modification of the ribose moiety, and any combination of the preceding.

Efficiency of guide strand (first polynucleotide) loading into the RISC complex might be altered for heavily modified polynucleotides, so in one embodiment, the duplex polynucleotide includes a mismatch between nucleotide 9, 11, 12, 13, or 14 on the guide strand (first polynucleotide) and the opposite nucleotide on the sense strand (second polynucleotide) to promote efficient guide strand loading.

More detailed aspects of the invention are described in the sections below.

Duplex Characteristics

Double-stranded oligonucleotides of the invention may be formed by two separate complementary nucleic acid strands. Duplex formation can occur either inside or outside the cell containing the target gene.

As used herein, the term "duplex" includes the region of the double-stranded nucleic acid molecule(s) that is (are) hydrogen bonded to a complementary sequence. Double-stranded oligonucleotides of the invention may comprise a nucleotide sequence that is sense to a target gene and a complementary sequence that is antisense to the target gene. The sense and antisense nucleotide sequences correspond to the target gene sequence, e.g., are identical or are sufficiently identical to effect target gene inhibition (e.g., are about at least about 98%

identical, 96% identical, 94%, 90% identical, 85% identical, or 80% identical) to the target gene sequence.

In certain embodiments, the double-stranded oligonucleotide of the invention is double-stranded over its entire length, i.e., with no overhanging single-stranded sequence at either end of the molecule, i.e., is blunt-ended. In other embodiments, the individual nucleic acid molecules can be of different lengths. In other words, a double-stranded oligonucleotide of the invention is not double-stranded over its entire length. For instance, when two separate nucleic acid molecules are used, one of the molecules, e.g., the first molecule comprising an antisense sequence, can be longer than the second molecule hybridizing thereto (leaving a portion of the molecule single-stranded). Likewise, when a single nucleic acid molecule is used a portion of the molecule at either end can remain single-stranded.

In one embodiment, a double-stranded oligonucleotide of the invention contains mismatches and/or loops or bulges, but is double-stranded over at least about 70% of the length of the oligonucleotide. In another embodiment, a double-stranded oligonucleotide of the invention is double-stranded over at least about 80% of the length of the oligonucleotide. In another embodiment, a double-stranded oligonucleotide of the invention is double-stranded over at least about 90%-95% of the length of the oligonucleotide. In another embodiment, a double-stranded oligonucleotide of the invention is double-stranded over at least about 96%-98% of the length of the oligonucleotide. In certain embodiments, the double-stranded oligonucleotide of the invention contains at least or up to 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, or 15 mismatches.

Modifications

The nucleotides of the invention may be modified at various locations, including the sugar moiety, the phosphodiester linkage, and/or the base.

Sugar moieties include natural, unmodified sugars, e.g., monosaccharide (such as pentose, e.g., ribose, deoxyribose), modified sugars and sugar analogs. In general, possible modifications of nucleomonomers, particularly of a sugar moiety, include, for example, replacement of one or more of the hydroxyl groups with a halogen, a heteroatom, an aliphatic group, or the functionalization of the hydroxyl group as an ether, an amine, a thiol, or the like.

One particularly useful group of modified nucleomonomers are 2'-O-methyl nucleotides. Such 2'-O-methyl nucleotides may be referred to as "methylated," and the corresponding nucleotides may be made from unmethylated nucleotides followed by alkylation or directly from methylated nucleotide reagents. Modified nucleomonomers may be used in combination with unmodified nucleomonomers. For example, an oligonucleotide of the invention may contain both methylated and unmethylated nucleomonomers.

Some exemplary modified nucleomonomers include sugar- or backbone-modified ribonucleotides. Modified ribonucleotides may contain a non-naturally occurring base (instead of a naturally occurring base), such as uridines or cytidines modified at the 5'-position, e.g., 5'-(2-amino)propyl uridine and 5'-bromo uridine; adenosines and guanosines modified at the 8-position, e.g., 8-bromo guanosine; deaza nucleotides, e.g., 7-deaza-adenosine; and N-alkylated nucleotides, e.g., N6-methyl adenosine. Also, sugar-modified ribonucleotides may have the 2'-OH group replaced by a H, alxoxy (or OR), R or alkyl, halogen, SH, SR, amino (such as NH_2, NHR, NR_2), or CN group, wherein R is lower alkyl, alkenyl, or alkynyl.

Modified ribonucleotides may also have the phosphodiester group connecting to adjacent ribonucleotides replaced by a modified group, e.g., of phosphorothioate group. More generally, the various nucleotide modifications may be combined.

Although the antisense (guide) strand may be substantially identical to at least a portion of the target gene (or genes), at least with respect to the base pairing properties, the sequence need not be perfectly identical to be useful, e.g., to inhibit expression of a target gene's phenotype. Generally, higher homology can be used to compensate for the use of a shorter antisense gene. In some cases, the antisense strand generally will be substantially identical (although in antisense orientation) to the target gene.

The use of 2'-O-methyl modified RNA may also be beneficial in circumstances in which it is desirable to minimize cellular stress responses. RNA having 2'-O-methyl nucleomonomers may not be recognized by cellular machinery that is thought to recognize unmodified RNA. The use of 2'-O-methylated or partially 2'-O-methylated RNA may avoid the interferon response to double-stranded nucleic acids, while maintaining target RNA inhibition. This may be useful, for example, for avoiding the interferon or other cellular stress responses, both in short RNAi (e.g., siRNA) sequences that induce the interferon response, and in longer RNAi sequences that may induce the interferon response.

Overall, modified sugars may include D-ribose, 2'-O-alkyl (including 2'-β-methyl and 2'-O-ethyl), i.e., 2'-alkoxy, 2'-amino, 2'-S-alkyl, 2'-halo (including 2'-fluoro), 2'-methoxyethoxy, 2'-allyloxy ($-OCH_2CH=CH_2$), 2'-propargyl, 2'-propyl, ethynyl, ethenyl, propenyl, and cyano and the like. In one embodiment, the sugar moiety can be a hexose and incorporated into an oligonucleotide as described (Augustyns, K., et al., *Nucl. Acids. Res.* 18:4711 (1992)). Exemplary nucleomonomers can be found, e.g., in U.S. Pat. No. 5,849,902, incorporated by reference herein.

The term "alkyl" includes saturated aliphatic groups, including straight-chain alkyl groups (e.g., methyl, ethyl, propyl, butyl, pentyl, hexyl, heptyl, octyl, nonyl, decyl, etc.), branched-chain alkyl groups (isopropyl, tert-butyl, isobutyl, etc.), cycloalkyl (alicyclic) groups (cyclopropyl, cyclopentyl, cyclohexyl, cycloheptyl, cyclooctyl), alkyl substituted cycloalkyl groups, and cycloalkyl substituted alkyl groups. In certain embodiments, a straight chain or branched chain alkyl has 6 or fewer carbon atoms in its backbone (e.g., C_1-C_6 for straight chain, C_3-C_6 for branched chain), and more preferably 4 or fewer. Likewise, preferred cycloalkyls have from 3-8 carbon atoms in their ring structure, and more preferably have 5 or 6 carbons in the ring structure. The term C_1-C_6 includes alkyl groups containing 1 to 6 carbon atoms.

Moreover, unless otherwise specified, the term alkyl includes both "unsubstituted alkyls" and "substituted alkyls," the latter of which refers to alkyl moieties having independently selected substituents replacing a hydrogen on one or more carbons of the hydrocarbon backbone. Such substituents can include, for example, alkenyl, alkynyl, halogen, hydroxyl, alkylcarbonyloxy, arylcarbonyloxy, alkoxycarbonyloxy, aryloxycarbonyloxy, carboxylate, alkylcarbonyl, arylcarbonyl, alkoxycarbonyl, aminocarbonyl, alkylaminocarbonyl, dialkylaminocarbonyl, alkylthiocarbonyl, alkoxyl, phosphate, phosphonato, phosphinato, cyano, amino (including alkyl amino, dialkylamino, arylamino, diarylamino, and alkylarylamino), acylamino (including alkylcarbonylamino, arylcarbonylamino, carbamoyl and ureido), amidino, imino, sulfhydryl, alkylthio, arylthio, thiocarboxylate, sulfates, alkylsulfinyl, sulfonato, sulfamoyl, sulfonamido, nitro, trifluoromethyl, cyano, azido, heterocyclyl, alkylaryl, or an aromatic or heteroaromatic moiety. Cycloalkyls can be further substituted, e.g., with the substituents described above. An "alkylaryl" or an "arylalkyl" moiety is an alkyl substituted with an aryl (e.g., phenylmethyl (benzyl)). The term "alkyl" also includes the side chains of natural and unnatural amino acids. The term "n-alkyl" means a straight chain (i.e., unbranched) unsubstituted alkyl group.

The term "alkenyl" includes unsaturated aliphatic groups analogous in length and possible substitution to the alkyls described above, but that contain at least one double bond. For example, the term "alkenyl" includes straight-chain alkenyl groups (e.g., ethylenyl, propenyl, butenyl, pentenyl, hexenyl, heptenyl, octenyl, nonenyl, decenyl, etc.), branched-chain alkenyl groups, cycloalkenyl (alicyclic) groups (cyclopropenyl, cyclopentenyl, cyclohexenyl, cycloheptenyl, cyclooctenyl), alkyl or alkenyl substituted cycloalkenyl groups, and cycloalkyl or cycloalkenyl substituted alkenyl groups. In certain embodiments, a straight chain or branched chain alkenyl group has 6 or fewer carbon atoms in its backbone (e.g., C_2-C_6 for straight chain, C_3-C_6 for branched chain). Likewise, cycloalkenyl groups may have from 3-8 carbon atoms in their ring structure, and more preferably have 5 or 6 carbons in the ring structure. The term C_2-C_6 includes alkenyl groups containing 2 to 6 carbon atoms.

Moreover, unless otherwise specified, the term alkenyl includes both "unsubstituted alkenyls" and "substituted alkenyls," the latter of which refers to alkenyl moieties having independently selected substituents replacing a hydrogen on one or more carbons of the hydrocarbon backbone. Such substituents can include, for example, alkyl groups, alkynyl groups, halogens, hydroxyl, alkylcarbonyloxy, arylcarbonyloxy, alkoxycarbonyloxy, aryloxycarbonyloxy, carboxylate, alkylcarbonyl, arylcarbonyl, alkoxycarbonyl, aminocarbonyl, alkylaminocarbonyl, dialkylaminocarbonyl, alkylthiocarbonyl, alkoxyl, phosphate, phosphonato, phosphinato, cyano, amino (including alkyl amino, dialkylamino, arylamino, diarylamino, and alkylarylamino), acylamino (including alkylcarbonylamino, arylcarbonylamino, carbamoyl and ureido), amidino, imino, sulfhydryl, alkylthio, arylthio, thiocarboxylate, sulfates, alkylsulfinyl, sulfonato, sulfamoyl, sulfonamido, nitro, trifluoromethyl, cyano, azido, heterocyclyl, alkylaryl, or an aromatic or heteroaromatic moiety.

The term "alkynyl" includes unsaturated aliphatic groups analogous in length and possible substitution to the alkyls described above, but which contain at least one triple bond. For example, the term "alkynyl" includes straight-chain alkynyl groups (e.g., ethynyl, propynyl, butynyl, pentynyl, hexynyl, heptynyl, octynyl, nonynyl, decynyl, etc.), branched-chain alkynyl groups, and cycloalkyl or cycloalkenyl substituted alkynyl groups. In certain embodiments, a straight chain or branched chain alkynyl group has 6 or fewer carbon atoms in its backbone (e.g., C_2-C_6 for straight chain, C_3-C_6 for branched chain). The term C_2-C_6 includes alkynyl groups containing 2 to 6 carbon atoms.

Moreover, unless otherwise specified, the term alkynyl includes both "unsubstituted alkynyls" and "substituted alkynyls," the latter of which refers to alkynyl moieties having independently selected substituents replacing a hydrogen on one or more carbons of the hydrocarbon backbone. Such substituents can include, for example, alkyl groups, alkynyl groups, halogens, hydroxyl, alkylcarbonyloxy, arylcarbonyloxy, alkoxycarbonyloxy, aryloxycarbonyloxy, carboxylate, alkylcarbonyl, arylcarbonyl, alkoxycarbonyl, aminocarbonyl, alkylaminocarbonyl, dialkylaminocarbonyl, alkylthiocarbonyl, alkoxyl, phosphate, phosphonato, phosphinato, cyano, amino (including alkyl amino, dialkylamino, arylamino, diarylamino, and alkylarylamino), acylamino (including alkylcarbonylamino, arylcarbonylamino, carbamoyl and ureido), amidino, imino, sulfhydryl, alkylthio, arylthio, thiocarboxylate, sulfates, alkylsulfinyl, sulfonato, sulfamoyl, sulfonamido, nitro, trifluoromethyl, cyano, azido, heterocyclyl, alkylaryl, or an aromatic or heteroaromatic moiety.

Unless the number of carbons is otherwise specified, "lower alkyl" as used herein means an alkyl group, as defined above, but having from one to five carbon atoms in its backbone structure. "Lower alkenyl" and "lower alkynyl" have chain lengths of, for example, 2-5 carbon atoms.

The term "alkoxy" includes substituted and unsubstituted alkyl, alkenyl, and alkynyl groups covalently linked to an oxygen atom. Examples of alkoxy groups include methoxy, ethoxy, isopropyloxy, propoxy, butoxy, and pentoxy groups. Examples of substituted alkoxy groups include halogenated alkoxy groups. The alkoxy groups can be substituted with independently selected groups such as alkenyl, alkynyl, halogen, hydroxyl, alkylcarbonyloxy, arylcarbonyloxy, alkoxycarbonyloxy, aryloxycarbonyloxy, carboxylate, alkylcarbonyl, arylcarbonyl, alkoxycarbonyl, aminocarbonyl, alkylaminocarbonyl, dialkylaminocarbonyl, alkylthiocarbonyl, alkoxyl, phosphate, phosphonato, phosphinato, cyano, amino (including alkyl amino, dialkylamino, arylamino, diarylamino, and alkylarylamino), acylamino (including alkylcarbonylamino, arylcarbonylamino, carbamoyl and ureido), amidino, imino, sulffiydryl, alkylthio, arylthio, thiocarboxylate, sulfates, alkylsulfinyl, sulfonato, sulfamoyl, sulfonamido, nitro, trifluoromethyl, cyano, azido, heterocyclyl, alkylaryl, or an aromatic or heteroaromatic moieties. Examples of halogen substituted alkoxy groups include, but are not limited to, fluoromethoxy, difluoromethoxy, trifluoromethoxy, chloromethoxy, dichloromethoxy, trichloromethoxy, etc.

The term "heteroatom" includes atoms of any element other than carbon or hydrogen. Preferred heteroatoms are nitrogen, oxygen, sulfur and phosphorus.

The term "hydroxy" or "hydroxyl" includes groups with an —OH or —O^- (with an appropriate counterion).

The term "halogen" includes fluorine, bromine, chlorine, iodine, etc. The term "perhalogenated" generally refers to a moiety wherein all hydrogens are replaced by halogen atoms.

The term "substituted" includes independently selected substituents which can be placed on the moiety and which allow the molecule to perform its intended function. Examples of substituents include alkyl, alkenyl, alkynyl, aryl, $(CR'R'')_{0-3}NR'R''$, $(CR'R'')_{0-3}CN$, NO_2, halogen, $(CR'R'')_{0-3}C(halogen)_3$, $(CR'R'')_{0-3}CH(halogen)_2$, $(CRR'')_{0-3}CH_2(halogen)$, $(CR'R'')_{0-3}CONR'R''$, $(CR'R'')_{0-3}S(O)_{1-2}NR'R''$, $(CR'R'')_{0-3}CHO$, $(CR'R'')_{0-3}O(CR'R'')_{0-3}H$, $(CR'R'')_{0-3}S(O)_{0-2}R'$, $(CR'R'')_{0-3}O(CR'R'')_{0-3}H$, $(CR'R'')_{0-3}COR'$, $(CR'R'')_{0-3}CO_2R'$, or $(CR'R'')_{0-3}OR'$ groups; wherein each R' and R'' are each independently hydrogen, a C_1-C_5 alkyl, C_2-C_5 alkenyl, C_2-C_5 alkynyl, or aryl group, or R' and R'' taken together are a benzylidene group or a —$(CH_2)_2$—O—$(CH_2)_2$— group.

The term "amine" or "amino" includes compounds or moieties in which a nitrogen atom is covalently bonded to at least one carbon or heteroatom. The term "alkyl amino" includes groups and compounds wherein the nitrogen is bound to at least one additional alkyl group. The term "dialkyl amino" includes groups wherein the nitrogen atom is bound to at least two additional alkyl groups.

The term "ether" includes compounds or moieties which contain an oxygen bonded to two different carbon atoms or heteroatoms. For example, the term includes "alkoxyalkyl," which refers to an alkyl, alkenyl, or alkynyl group covalently bonded to an oxygen atom which is covalently bonded to another alkyl group.

The term "base" includes the known purine and pyrimidine heterocyclic bases, deazapurines, and analogs (including heterocyclic substituted analogs, e.g., aminoethyoxy phenoxazine), derivatives (e.g., 1-alkyl-, 1-alkenyl-, heteroaromatic- and 1-alkynyl derivatives) and tautomers thereof. Examples of purines include adenine, guanine, inosine, diaminopurine, and xanthine and analogs (e.g., 8-oxo-N^6-methyladenine or 7-diazaxanthine) and derivatives thereof. Pyrimidines include, for example, thymine, uracil, and cytosine, and their analogs (e.g., 5-methylcytosine, 5-methyluracil, 5-(1-propynyl)uracil, 5-(1-propynyl)cytosine and 4,4-ethanocytosine). Other examples of suitable bases include non-purinyl and non-pyrimidinyl bases such as 2-aminopyridine and triazines.

In a preferred embodiment, the nucleomonomers of an oligonucleotide of the invention are RNA nucleotides. In another preferred embodiment, the nucleomonomers of an oligonucleotide of the invention are modified RNA nucleotides. Thus, the oligonucleotides contain modified RNA nucleotides.

The term "nucleoside" includes bases which are covalently attached to a sugar moiety, preferably ribose or deoxyribose. Examples of preferred nucleosides include ribonucleosides and deoxyribonucleosides. Nucleosides also include bases linked to amino acids or amino acid analogs which may comprise free carboxyl groups, free amino groups, or protecting groups. Suitable protecting groups are well known in the art (see P. G. M. Wuts and T. W. Greene, "Protective Groups in Organic Synthesis", 2nd Ed., Wiley-Interscience, New York, 1999).

The term "nucleotide" includes nucleosides which further comprise a phosphate group or a phosphate analog.

As used herein, the term "linkage" includes a naturally occurring, unmodified phosphodiester moiety (—O—(PO^{2-})—O—) that covalently couples adjacent nucleomonomers. As used herein, the term "substitute linkage" includes any analog or derivative of the native phosphodiester group that covalently couples adjacent nucleomonomers. Substitute linkages include phosphodiester analogs, e.g., phosphorothioate, phosphorodithioate, and P-ethyoxyphosphodiester, P-ethoxyphosphodiester, P-alkyloxyphosphotriester, methylphosphonate, and nonphosphorus containing linkages, e.g., acetals and amides. Such substitute linkages are known in the art (e.g., Bjergarde et al. 1991. Nucleic Acids Res. 19:5843; Caruthers et al. 1991. Nucleosides Nucleotides. 10:47). In certain embodiments, non-hydrolizable linkages are preferred, such as phosphorothiate linkages.

In certain embodiments, oligonucleotides of the invention comprise hydrophobicly modified nucleotides or "hydrophobic modifications." As used herein "hydrophobic modifications" refers to bases that are modified such that (1) overall hydrophobicity of the base is significantly increased, and/or (2) the base is still capable of forming close to regular Watson-Crick interaction. Several non-limiting examples of base modifications include 5-position uridine and cytidine modifications such as phenyl, 4-pyridyl, 2-pyridyl, indolyl, and isobutyl, phenyl (C6H5OH); tryptophanyl (C8H6N)CH2CH(NH_2)CO), Isobutyl, butyl, aminobenzyl; phenyl; and naphthyl.

In certain embodiments, oligonucleotides of the invention comprise 3' and 5' termini (except for circular oligonucleotides). In one embodiment, the 3' and 5' termini of an oligonucleotide can be substantially protected from nucleases e.g., by modifying the 3' or 5' linkages (e.g., U.S. Pat. No. 5,849,902 and WO 98/13526). For example, oligonucleotides can be made resistant by the inclusion of a "blocking group." The term "blocking group" as used herein refers to substituents (e.g., other than OH groups) that can be attached to oligonucleotides or nucleomonomers, either as protecting groups or coupling groups for synthesis (e.g., FITC, propyl (CH_2—CH_2—CH_3), glycol (—O—CH_2—CH_2—O—) phosphate (PO_3^{2-}), hydrogen phosphonate, or phosphoramidite). "Blocking groups" also include "end blocking groups" or "exonuclease blocking groups" which protect the 5' and 3' termini of the oligonucleotide, including modified nucleotides and non-nucleotide exonuclease resistant structures.

Exemplary end-blocking groups include cap structures (e.g., a 7-methylguanosine cap), inverted nucleomonomers, e.g., with 3'-3' or 5'-5' end inversions (see, e.g., Ortiagao et al. 1992. *Antisense Res. Dev.* 2:129), methylphosphonate, phosphoramidite, non-nucleotide groups (e.g., non-nucleotide linkers, amino linkers, conjugates) and the like. The 3' terminal nucleomonomer can comprise a modified sugar moiety. The 3' terminal nucleomonomer comprises a 3'-O that can optionally be substituted by a blocking group that prevents 3'-exonuclease degradation of the oligonucleotide. For example, the 3'-hydroxyl can be esterified to a nucleotide through a 3'→3' internucleotide linkage. For example, the alkyloxy radical can be methoxy, ethoxy, or isopropoxy, and preferably, ethoxy. Optionally, the 3'→3' linked nucleotide at the 3' terminus can be linked by a substitute linkage. To reduce nuclease degradation, the 5' most 3'→5' linkage can be a modified linkage, e.g., a phosphorothioate or a P-alkyloxyphosphotriester linkage. Preferably, the two 5' most 3'→5' linkages are modified linkages. Optionally, the 5' terminal hydroxy moiety can be esterified with a phosphorus containing moiety, e.g., phosphate, phosphorothioate, or P-ethoxyphosphate.

Another type of conjugates that can be attached to the end (3' or 5' end), the loop region, or any other parts of the miniRNA might include a sterol, sterol type molecule, peptide, small molecule, protein, etc. In some embodiments, a miniRNA may contain more than one conjugates (same or different chemical nature). In some embodiments, the conjugate is cholesterol.

Another way to increase target gene specificity, or to reduce off-target silencing effect, is to introduce a 2'-modification (such as the 2'-O methyl modification) at a position corresponding to the second 5'-end nucleotide of the guide sequence. This allows the positioning of this 2'-modification in the Dicer-resistant hairpin structure, thus enabling one to design better RNAi constructs with less or no off-target silencing.

In one embodiment, a hairpin polynucleotide of the invention can comprise one nucleic acid portion which is DNA and one nucleic acid portion which is RNA. Antisense (guide) sequences of the invention can be "chimeric oligonucleotides" which comprise an RNA-like and a DNA-like region.

The language "RNase H activating region" includes a region of an oligonucleotide, e.g., a chimeric oligonucleotide, that is capable of recruiting RNase H to cleave the target RNA strand to which the oligonucleotide binds. Typically, the RNase activating region contains a minimal core (of at least about 3-5, typically between about 3-12, more typically, between about 5-12, and more preferably between about 5-10 contiguous nucleomonomers) of DNA or DNA-like nucleomonomers. (See, e.g., U.S. Pat. No. 5,849,902). Preferably, the RNase H activating region comprises about nine contiguous deoxyribose containing nucleomonomers.

The language "non-activating region" includes a region of an antisense sequence, e.g., a chimeric oligonucleotide, that does not recruit or activate RNase H. Preferably, a non-activating region does not comprise phosphorothioate DNA. The oligonucleotides of the invention comprise at least one non-activating region. In one embodiment, the non-activating region can be stabilized against nucleases or can provide specificity for the target by being complementary to the target and forming hydrogen bonds with the target nucleic acid molecule, which is to be bound by the oligonucleotide.

In one embodiment, at least a portion of the contiguous polynucleotides are linked by a substitute linkage, e.g., a phosphorothioate linkage.

In certain embodiments, most or all of the nucleotides beyond the guide sequence (2'-modified or not) are linked by phosphorothioate linkages. Such constructs tend to have improved pharmacokinetics due to their higher affinity for serum proteins. The phosphorothioate linkages in the non-guide sequence portion of the polynucleotide generally do not interfere with guide strand activity, once the latter is loaded into RISC.

Antisense (guide) sequences of the present invention may include "morpholino oligonucleotides." Morpholino oligonucleotides are non-ionic and function by an RNase H-independent mechanism. Each of the 4 genetic bases (Adenine, Cytosine, Guanine, and Thymine/Uracil) of the morpholino oligonucleotides is linked to a 6-membered morpholine ring. Morpholino oligonucleotides are made by joining the 4 different subunit types by, e.g., non-ionic phosphorodiamidate inter-subunit linkages. Morpholino oligonucleotides have many advantages including: complete resistance to nucleases (Antisense & Nucl. Acid Drug Dev. 1996. 6:267); predictable targeting (Biochemica Biophysica Acta. 1999. 1489:141); reliable activity in cells (Antisense & Nucl. Acid Drug Dev. 1997. 7:63); excellent sequence specificity (Antisense & Nucl. Acid Drug Dev. 1997. 7:151); minimal non-antisense activity (Biochemica Biophysica Acta. 1999. 1489:141); and simple osmotic or scrape delivery (Antisense & Nucl. Acid Drug Dev. 1997. 7:291). Morpholino oligonucleotides are also preferred because of their non-toxicity at high doses. A discussion of the preparation of morpholino oligonucleotides can be found in Antisense & Nucl. Acid Drug Dev. 1997. 7:187.

The chemical modifications described herein are believed, based on the data described herein, to promote single stranded polynucleotide loading into the RISC. Single stranded polynucleotides have been shown to be active in loading into RISC and inducing gene silencing. However, the level of activity for single stranded polynucleotides appears to be 2 to 4 orders of magnitude lower when compared to a duplex polynucleotide.

The present invention provides a description of the chemical modification patterns, which may (a) significantly increase stability of the single stranded polynucleotide (b) promote efficient loading of the polynucleotide into the RISC complex and (c) improve uptake of the single stranded nucleotide by the cell. FIG. **5** provides some non-limiting examples of the chemical modification patterns which may be beneficial for achieving single stranded polynucleotide efficacy inside the cell. The chemical modification patterns may include combination of ribose, backbone, hydrophobic nucleoside and conjugate type of modifications. In addition, in some of the embodiments, the 5' end of the single polynucleotide may be chemically phosphorylated.

In yet another embodiment, the present invention provides a description of the chemical modifications patterns, which improve functionality of RISC inhibiting polynucleotides. Single stranded polynucleotides have been shown to inhibit activity of a preloaded RISC complex through the substrate competition mechanism. For these types of molecules, conventionally called antagomers, the activity usually requires high concentration and in vivo delivery is not very effective. The present invention provides a description of the chemical modification patterns, which may (a) significantly increase stability of the single stranded polynucleotide (b) promote efficient recognition of the polynucleotide by the RISC as a substrate and/or (c) improve uptake of the single stranded nucleotide by the cell. FIG. **6** provides some non-limiting examples of the chemical modification patterns that may be beneficial for achieving single stranded polynucleotide efficacy inside the cell. The chemical modification patterns may include combination of ribose, backbone, hydrophobic nucleoside and conjugate type of modifications.

The modifications provided by the present invention are applicable to all polynucleotides. This includes single stranded RISC entering polynucleotides, single stranded RISC inhibiting polynucleotides, conventional duplexed polynucleotides of variable length (15-40 bp), asymmetric duplexed polynucleotides, and the like. Polynucleotides may be modified with wide variety of chemical modification patterns, including 5' end, ribose, backbone and hydrophobic nucleoside modifications.

Synthesis

Oligonucleotides of the invention can be synthesized by any method known in the art, e.g., using enzymatic synthesis and/or chemical synthesis. The oligonucleotides can be synthesized in vitro (e.g., using enzymatic synthesis and chemical synthesis) or in vivo (using recombinant DNA technology well known in the art).

In a preferred embodiment, chemical synthesis is used for modified polynucleotides. Chemical synthesis of linear oligonucleotides is well known in the art and can be achieved by solution or solid phase techniques. Preferably, synthesis is by solid phase methods. Oligonucleotides can be made by any of several different synthetic procedures including the phosphoramidite, phosphite triester, H-phosphonate, and phosphotriester methods, typically by automated synthesis methods.

Oligonucleotide synthesis protocols are well known in the art and can be found, e.g., in U.S. Pat. No. 5,830,653; WO 98/13526; Stec et al. 1984. *J. Am. Chem. Soc.* 106:6077; Stec et al. 1985. *J. Org. Chem.* 50:3908; Stec et al. J. Chromatog. 1985. 326:263; LaPlanche et al. 1986. *Nucl. Acid. Res.* 1986. 14:9081; Fasman G. D., 1989. Practical Handbook of Biochemistry and Molecular Biology. 1989. CRC Press, Boca Raton, Fla.; Lamone. 1993. *Biochem. Soc. Trans.* 21:1; U.S. Pat. No. 5,013,830; U.S. Pat. No. 5,214,135; U.S. Pat. No. 5,525,719; Kawasaki et al. 1993. *J. Med. Chem.* 36:831; WO 92/03568; U.S. Pat. No. 5,276,019; and U.S. Pat. No. 5,264,423.

The synthesis method selected can depend on the length of the desired oligonucleotide and such choice is within the skill of the ordinary artisan. For example, the phosphoramidite and phosphite triester method can produce oligonucleotides having 175 or more nucleotides, while the H-phosphonate method works well for oligonucleotides of less than 100 nucleotides. If modified bases are incorporated into the oligonucleotide, and particularly if modified phosphodiester linkages are used, then the synthetic procedures are altered as needed according to known procedures. In this regard, Uhlmann et al. (1990, *Chemical Reviews* 90:543-584) provide references and outline procedures for making oligonucleotides with modified bases and modified phosphodiester linkages. Other exemplary methods for making oligonucleotides are taught in Sonveaux. 1994. "Protecting Groups in Oligonucleotide Synthesis"; Agrawal. *Methods in Molecular Biology* 26:1. Exemplary synthesis methods are also taught in "Oligonucleotide Synthesis—A Practical Approach" (Gait, M. J. IRL Press at Oxford University Press. 1984). Moreover, linear oligonucleotides of defined sequence, including some sequences with modified nucleotides, are readily available from several commercial sources.

The oligonucleotides may be purified by polyacrylamide gel electrophoresis, or by any of a number of chromatographic methods, including gel chromatography and high pressure liquid chromatography. To confirm a nucleotide sequence, especially unmodified nucleotide sequences, oligonucleotides may be subjected to DNA sequencing by any of the known procedures, including Maxam and Gilbert sequencing, Sanger sequencing, capillary electrophoresis sequencing, the wandering spot sequencing procedure or by using selective chemical degradation of oligonucleotides bound to Hybond paper. Sequences of short oligonucleotides can also be analyzed by laser desorption mass spectroscopy or by fast atom bombardment (McNeal, et al., 1982, *J. Am. Chem. Soc.* 104:976; Viari, et al., 1987, *Biomed. Environ. Mass Spectrom.* 14:83; Grotjahn et al., 1982, *Nuc. Acid Res.* 10:4671). Sequencing methods are also available for RNA oligonucleotides.

The quality of oligonucleotides synthesized can be verified by testing the oligonucleotide by capillary electrophoresis and denaturing strong anion HPLC(SAX-HPLC) using, e.g., the method of Bergot and Egan. 1992. *J. Chrom.* 599:35.

Other exemplary synthesis techniques are well known in the art (see, e.g., Sambrook et al., Molecular Cloning: a Laboratory Manual, Second Edition (1989); DNA Cloning, Volumes I and II (D N Glover Ed. 1985); Oligonucleotide Synthesis (M J Gait Ed, 1984; Nucleic Acid Hybridisation (B D Hames and S J Higgins eds. 1984); A Practical Guide to Molecular Cloning (1984); or the series, Methods in Enzymology (Academic Press, Inc.)).

In certain embodiments, the subject RNAi constructs or at least portions thereof are transcribed from expression vectors encoding the subject constructs. Any art recognized vectors may be use for this purpose. The transcribed RNAi constructs may be isolated and purified, before desired modifications (such as replacing an unmodified sense strand with a modified one, etc.) are carried out.

Delivery/Carrier

Uptake of Oligonucleotides by Cells

Oligonucleotides and oligonucleotide compositions are contacted with (i.e., brought into contact with, also referred to herein as administered or delivered to) and taken up by one or more cells or a cell lysate. The term “cells” includes prokaryotic and eukaryotic cells, preferably vertebrate cells, and, more preferably, mammalian cells. In a preferred embodiment, the oligonucleotide compositions of the invention are contacted with human cells.

Oligonucleotide compositions of the invention can be contacted with cells in vitro, e.g., in a test tube or culture dish, (and may or may not be introduced into a subject) or in vivo, e.g., in a subject such as a mammalian subject. Oligonucleotides are taken up by cells at a slow rate by endocytosis, but endocytosed oligonucleotides are generally sequestered and not available, e.g., for hybridization to a target nucleic acid molecule. In one embodiment, cellular uptake can be facilitated by electroporation or calcium phosphate precipitation. However, these procedures are only useful for in vitro or ex vivo embodiments, are not convenient and, in some cases, are associated with cell toxicity.

In another embodiment, delivery of oligonucleotides into cells can be enhanced by suitable art recognized methods including calcium phosphate, DMSO, glycerol or dextran, electroporation, or by transfection, e.g., using cationic, anionic, or neutral lipid compositions or liposomes using methods known in the art (see e.g., WO 90/14074; WO 91/16024; WO 91/17424; U.S. Pat. No. 4,897,355; Bergan et al. 1993. *Nucleic Acids Research.* 21:3567). Enhanced delivery of oligonucleotides can also be mediated by the use of vectors (See e.g., Shi, Y. 2003. Trends Genet. 2003 Jan. 19:9; Reichhart J M et al. Genesis. 2002. 34(1-2):1604, Yu et al. 2002. Proc. Natl. Acad. Sci. USA 99:6047; Sui et al. 2002. Proc. Natl. Acad. Sci. USA 99:5515) viruses, polyamine or polycation conjugates using compounds such as polylysine, protamine, or Ni, N12-bis(ethyl) spermine (see, e.g., Bartzatt, R. et al. 1989. *Biotechnol. Appl. Biochem.* 11:133; Wagner E. et al. 1992. *Proc. Natl. Acad. Sci.* 88:4255).

In certain embodiments, the miniRNA of the invention may be delivered by using various beta-glucan containing particles, such as those described in US 2005/0281781 A1, WO 2006/007372, and WO 2007/050643 (all incorporated herein by reference). In certain embodiments, the beta-glucan particle is derived from yeast. In certain embodiments, the payload trapping molecule is a polymer, such as those with a molecular weight of at least about 1000 Da, 10,000 Da, 50,000 Da, 100 kDa, 500 kDa, etc. Preferred polymers include (without limitation) cationic polymers, chitosans, or PEI (polyethylenimine), etc.

Such beta-glucan based delivery system may be formulated for oral delivery, where the orally delivered beta-glucan/miniRNA constructs may be engulfed by macrophages or other related phagocytic cells, which may in turn release the miniRNA constructs in selected in vivo sites. Alternatively or in addition, the miniRNA may changes the expression of certain macrophage target genes.

The optimal protocol for uptake of oligonucleotides will depend upon a number of factors, the most crucial being the type of cells that are being used. Other factors that are important in uptake include, but are not limited to, the nature and concentration of the oligonucleotide, the confluence of the cells, the type of culture the cells are in (e.g., a suspension culture or plated) and the type of media in which the cells are grown.

Encapsulating Agents

Encapsulating agents entrap oligonucleotides within vesicles. In another embodiment of the invention, an oligonucleotide may be associated with a carrier or vehicle, e.g., liposomes or micelles, although other carriers could be used, as would be appreciated by one skilled in the art. Liposomes are vesicles made of a lipid bilayer having a structure similar to biological membranes. Such carriers are used to facilitate the cellular uptake or targeting of the oligonucleotide, or improve the oligonucleotide’s pharmacokinetic or toxicologic properties.

For example, the oligonucleotides of the present invention may also be administered encapsulated in liposomes, pharmaceutical compositions wherein the active ingredient is contained either dispersed or variously present in corpuscles consisting of aqueous concentric layers adherent to lipidic layers. The oligonucleotides, depending upon solubility, may be present both in the aqueous layer and in the lipidic layer, or in what is generally termed a liposomic suspension. The hydrophobic layer, generally but not exclusively, comprises phopholipids such as lecithin and sphingomyelin, steroids such as cholesterol, more or less ionic surfactants such as diacetylphosphate, stearylamine, or phosphatidic acid, or other materials of a hydrophobic nature. The diameters of the liposomes generally range from about 15 nm to about 5 microns.

The use of liposomes as drug delivery vehicles offers several advantages. Liposomes increase intracellular stability, increase uptake efficiency and improve biological activity. Liposomes are hollow spherical vesicles composed of lipids arranged in a similar fashion as those lipids which make up the cell membrane. They have an internal aqueous space for entrapping water soluble compounds and range in size from

0.05 to several microns in diameter. Several studies have shown that liposomes can deliver nucleic acids to cells and that the nucleic acids remain biologically active. For example, a lipid delivery vehicle originally designed as a research tool, such as Lipofectin or LIPOFECTAMINE™ 2000, can deliver intact nucleic acid molecules to cells.

Specific advantages of using liposomes include the following: they are non-toxic and biodegradable in composition; they display long circulation half-lives; and recognition molecules can be readily attached to their surface for targeting to tissues. Finally, cost-effective manufacture of liposome-based pharmaceuticals, either in a liquid suspension or lyophilized product, has demonstrated the viability of this technology as an acceptable drug delivery system.

In some aspects, formulations associated with the invention might be selected for a class of naturally occurring or chemically synthesized or modified saturated and unsaturated fatty acid residues. Fatty acids might exist in a form of triglycerides, diglycerides or individual fatty acids. In another embodiment, the use of well-validated mixtures of fatty acids and/or fat emulsions currently used in pharmacology for parenteral nutrition may be utilized.

Liposome based formulations are widely used for oligonucleotide delivery. However, most of commercially available lipid or liposome formulations contain at least one positively charged lipid (cationic lipids). The presence of this positively charged lipid is believed to be essential for obtaining a high degree of oligonucleotide loading and for enhancing liposome fusogenic properties. Several methods have been performed and published to identify optimal positively charged lipid chemistries. However, the commercially available liposome formulations containing cationic lipids are characterized by a high level of toxicity. In vivo limited therapeutic indexes have revealed that liposome formulations containing positive charged lipids are associated with toxicity (i.e. elevation in liver enzymes) at concentrations only slightly higher than concentration required to achieve RNA silencing.

New liposome formulations, lacking the toxicity of the prior art liposomes have been developed according to the invention. These new liposome formulations are neutral fat-based formulations for the efficient delivery of oligonucleotides, and in particular for the delivery of the RNA molecules of the invention. The compositions are referred to as neutral nanotransporters because they enable quantitative oligonucleotide incorporation into non-charged lipids mixtures. The lack of toxic levels of cationic lipids in the neutral nanotransporter compositions of the invention is an important feature.

The neutral nanotransporters compositions enable efficient loading of oligonucleotide into neutral fat formulation. The composition includes an oligonucleotide that is modified in a manner such that the hydrophobicity of the molecule is increased (for example a hydrophobic molecule is attached (covalently or no-covalently) to a hydrophobic molecule on the oligonucleotide terminus or a non-terminal nucleotide, base, sugar, or backbone), the modified oligonucleotide being mixed with a neutral fat formulation (for example containing at least 25% of cholesterol and 25% of DOPC or analogs thereof). A cargo molecule, such as another lipid can also be included in the composition. This composition, where part of the formulation is build into the oligonucleotide itself, enables efficient encapsulation of oligonucleotide in neutral lipid particles.

One of several unexpected observations associated with the invention was that the oligonucleotides of the invention could effectively be incorporated in a lipid mixture that was free of cationic lipids and that such a composition could effectively deliver the therapeutic oligonucleotide to a cell in a manner that it is functional. Another unexpected observation was the high level of activity observed when the fatty mixture is composed of a phosphatidylcholine base fatty acid and a sterol such as a cholesterol. For instance, one preferred formulation of neutral fatty mixture is composed of at least 20% of DOPC or DSPC and at least 20% of sterol such as cholesterol. Even as low as 1:5 lipid to oligonucleotide ratio was shown to be sufficient to get complete encapsulation of the oligonucleotide in a non charged formulation. The prior art demonstrated only a 1-5% oligonucleotide encapsulation with non-charged formulations, which is not sufficient to get to a desired amount of in vivo efficacy. Compared to the prior art using neutral lipids the level of oligonucleotide delivery to a cell was quite unexpected.

Stable particles ranging in size from 50 to 140 nm were formed upon complexing of hydrophobic oligonucleotides with preferred formulations. It is interesting to mention that the formulation by itself typically does not form small particles, but rather, forms agglomerates, which are transformed into stable 50-120 nm particles upon addition of the hydrophobic modified oligonucleotide.

The neutral nanotransporter compositions of the invention include a hydrophobic modified polynucleotide, a neutral fatty mixture, and optionally a cargo molecule. A "hydrophobic modified polynucleotide" as used herein is a polynucleotide of the invention (i.e. sd-rxRNA) that has at least one modification that renders the polynucleotide more hydrophobic than the polynucleotide was prior to modification. The modification may be achieved by attaching (covalently or non-covalently) a hydrophobic molecule to the polynucleotide. In some instances the hydrophobic molecule is or includes a lipophilic group.

The term "lipophilic group" means a group that has a higher affinity for lipids than its affinity for water. Examples of lipophilic groups include, but are not limited to, cholesterol, a cholesteryl or modified cholesteryl residue, adamantine, dihydrotesterone, long chain alkyl, long chain alkenyl, long chain alkynyl, olely-lithocholic, cholenic, oleoyl-cholenic, palmityl, heptadecyl, myrisityl, bile acids, cholic acid or taurocholic acid, deoxycholate, oleyl litocholic acid, oleoyl cholenic acid, glycolipids, phospholipids, sphingolipids, isoprenoids, such as steroids, vitamins, such as vitamin E, fatty acids either saturated or unsaturated, fatty acid esters, such as triglycerides, pyrenes, porphyrines, Texaphyrine, adamantane, acridines, biotin, coumarin, fluorescein, rhodamine, Texas-Red, digoxygenin, dimethoxytrityl, t-butyldimethylsilyl, t-butyldiphenylsilyl, cyanine dyes (e.g. Cy3 or Cy5), Hoechst 33258 dye, psoralen, or ibuprofen. The cholesterol moiety may be reduced (e.g. as in cholestan) or may be substituted (e.g. by halogen). A combination of different lipophilic groups in one molecule is also possible.

The hydrophobic molecule may be attached at various positions of the polynucleotide. As described above, the hydrophobic molecule may be linked to the terminal residue of the polynucleotide such as the 3' of 5'-end of the polynucleotide. Alternatively, it may be linked to an internal nucleotide or a nucleotide on a branch of the polynucleotide. The hydrophobic molecule may be attached, for instance to a 2'-position of the nucleotide. The hydrophobic molecule may also be linked to the heterocyclic base, the sugar or the backbone of a nucleotide of the polynucleotide.

The hydrophobic molecule may be connected to the polynucleotide by a linker moiety. Optionally the linker moiety is a non-nucleotidic linker moiety. Non-nucleotidic linkers are e.g. abasic residues (dSpacer), oligoethyleneglycol, such as triethyleneglycol (spacer 9) or hexaethylenegylcol (spacer 18), or alkane-diol, such as butanediol. The spacer units are preferably linked by phosphodiester or phosphorothioate bonds. The linker units may appear just once in the molecule or may be incorporated several times, e.g. via phosphodiester, phosphorothioate, methylphosphonate, or amide linkages.

Typical conjugation protocols involve the synthesis of polynucleotides bearing an aminolinker at one or more positions of the sequence, however, a linker is not required. The amino group is then reacted with the molecule being conjugated using appropriate coupling or activating reagents. The conjugation reaction may be performed either with the polynucleotide still bound to a solid support or following cleavage of the polynucleotide in solution phase. Purification of the modified polynucleotide by HPLC typically results in a pure material.

In some embodiments the hydrophobic molecule is a sterol type conjugate, a PhytoSterol conjugate, cholesterol conjugate, sterol type conjugate with altered side chain length, fatty acid conjugate, any other hydrophobic group conjugate, and/or hydrophobic modifications of the internal nucleoside, which provide sufficient hydrophobicity to be incorporated into micelles.

For purposes of the present invention, the term "sterols", refers or steroid alcohols are a subgroup of steroids with a hydroxyl group at the 3-position of the A-ring. They are amphipathic lipids synthesized from acetyl-coenzyme A via the HMG-CoA reductase pathway. The overall molecule is quite flat. The hydroxyl group on the A ring is polar. The rest of the aliphatic chain is non-polar. Usually sterols are considered to have an 8 carbon chain at position 17.

For purposes of the present invention, the term "sterol type molecules", refers to steroid alcohols, which are similar in structure to sterols. The main difference is the structure of the ring and number of carbons in a position 21 attached side chain.

For purposes of the present invention, the term "PhytoSterols" (also called plant sterols) are a group of steroid alcohols, phytochemicals naturally occurring in plants. There are more then 200 different known PhytoSterols

For purposes of the present invention, the term "Sterol side chain" refers to a chemical composition of a side chain attached at the position 17 of sterol-type molecule. In a standard definition sterols are limited to a 4 ring structure carrying a 8 carbon chain at position 17. In this invention, the sterol type molecules with side chain longer and shorter than conventional are described. The side chain may branched or contain double back bones.

Thus, sterols useful in the invention, for example, include cholesterols, as well as unique sterols in which position 17 has attached side chain of 2-7 or longer then 9 carbons. In a particular embodiment, the length of the polycarbon tail is varied between 5 and 9 carbons. FIG. **9** demonstrates that there is a correlation between plasma clearance, liver uptake and the length of the polycarbon chain. Such conjugates may have significantly better in vivo efficacy, in particular delivery to liver. These types of molecules are expected to work at concentrations 5 to 9 fold lower then oligonucleotides conjugated to conventional cholesterols.

Alternatively the polynucleotide may be bound to a protein, peptide or positively charged chemical that functions as the hydrophobic molecule. The proteins may be selected from the group consisting of protamine, dsRNA binding domain, and arginine rich peptides. Exemplary positively charged chemicals include spermine, spermidine, cadaverine, and putrescine.

In another embodiment hydrophobic molecule conjugates may demonstrate even higher efficacy when it is combined with optimal chemical modification patterns of the polynucleotide (as described herein in detail), containing but not limited to hydrophobic modifications, phosphorothioate modifications, and 2' ribo modifications.

In another embodiment the sterol type molecule may be a naturally occurring PhytoSterols such as those shown in FIG. **8**. The polycarbon chain may be longer than 9 and may be linear, branched and/or contain double bonds. Some PhytoSterol containing polynucleotide conjugates may be significantly more potent and active in delivery of polynucleotides to various tissues. Some PhytoSterols may demonstrate tissue preference and thus be used as a way to delivery RNAi specifically to particular tissues.

The hydrophobic modified polynucleotide is mixed with a neutral fatty mixture to form a micelle. The neutral fatty acid mixture is a mixture of fats that has a net neutral or slightly net negative charge at or around physiological pH that can form a micelle with the hydrophobic modified polynucleotide. For purposes of the present invention, the term "micelle" refers to a small nanoparticle formed by a mixture of non charged fatty acids and phospholipids. The neutral fatty mixture may include cationic lipids as long as they are present in an amount that does not cause toxicity. In preferred embodiments the neutral fatty mixture is free of cationic lipids. A mixture that is free of cationic lipids is one that has less than 1% and preferably 0% of the total lipid being cationic lipid. The term "cationic lipid" includes lipids and synthetic lipids having a net positive charge at or around physiological pH. The term "anionic lipid" includes lipids and synthetic lipids having a net negative charge at or around physiological pH.

The neutral fats bind to the oligonucleotides of the invention by a strong but non-covalent attraction (e.g., an electrostatic, van der Waals, pi-stacking, etc. interaction).

The neutral fat mixture may include formulations selected from a class of naturally occurring or chemically synthesized or modified saturated and unsaturated fatty acid residues. Fatty acids might exist in a form of triglycerides, diglycerides or individual fatty acids. In another embodiment the use of well-validated mixtures of fatty acids and/or fat emulsions currently used in pharmacology for parenteral nutrition may be utilized.

The neutral fatty mixture is preferably a mixture of a choline based fatty acid and a sterol. Choline based fatty acids include for instance, synthetic phosphocholine derivatives such as DDPC, DLPC, DMPC, DPPC, DSPC, DOPC, POPC, and DEPC. DOPC (chemical registry number 4235-95-4) is dioleoylphosphatidylcholine (also known as dielaidoylphosphatidylcholine, dioleoyl-PC, dioleoylphosphocholine, dioleoyl-sn-glycero-3-phosphocholine, dioleylphosphatidylcholine). DSPC (chemical registry number 816-94-4) is distearoylphosphatidylcholine (also known as 1,2-Distearoyl-sn-Glycero-3-phosphocholine).

The sterol in the neutral fatty mixture may be for instance cholesterol. The neutral fatty mixture may be made up completely of a choline based fatty acid and a sterol or it may optionally include a cargo molecule. For instance, the neutral fatty mixture may have at least 20% or 25% fatty acid and 20% or 25% sterol.

For purposes of the present invention, the term "Fatty acids" relates to conventional description of fatty acid. They may exist as individual entities or in a form of two- and triglycerides. For purposes of the present invention, the term "fat emulsions" refers to safe fat formulations given intravenously to subjects who are unable to get enough fat in their diet. It is an emulsion of soy bean oil (or other naturally occurring oils) and egg phospholipids. Fat emulsions are being used for formulation of some insoluble anesthetics. In this disclosure, fat emulsions might be part of commercially available preparations like Intralipid, Liposyn, Nutrilipid, modified commercial preparations, where they are enriched with particular fatty acids or fully de novo-formulated combinations of fatty acids and phospholipids.

In one embodiment, the cells to be contacted with an oligonucleotide composition of the invention are contacted with a mixture comprising the oligonucleotide and a mixture comprising a lipid, e.g., one of the lipids or lipid compositions described supra for between about 12 hours to about 24 hours. In another embodiment, the cells to be contacted with an oligonucleotide composition are contacted with a mixture comprising the oligonucleotide and a mixture comprising a lipid, e.g., one of the lipids or lipid compositions described supra for between about 1 and about five days. In one embodiment, the cells are contacted with a mixture comprising a lipid and the oligonucleotide for between about three days to as long as about 30 days. In another embodiment, a mixture comprising a lipid is left in contact with the cells for at least about five to about 20 days. In another embodiment, a mixture comprising a lipid is left in contact with the cells for at least about seven to about 15 days.

50%-60% of the formulation can optionally be any other lipid or molecule. Such a lipid or molecule is referred to herein as a cargo lipid or cargo molecule. Cargo molecules include but are not limited to intralipid, small molecules, fusogenic peptides or lipids or other small molecules might be added to alter cellular uptake, endosomal release or tissue distribution properties. The ability to tolerate cargo molecules is important for modulation of properties of these particles, if such properties are desirable. For instance the presence of some tissue specific metabolites might drastically alter tissue distribution profiles. For example use of Intralipid type formulation enriched in shorter or longer fatty chains with various degrees of saturation affects tissue distribution profiles of these type of formulations (and their loads).

An example of a cargo lipid useful according to the invention is a fusogenic lipid. For instance, the zwiterionic lipid DOPE (chemical registry number 4004-5-1,1,2-Dioleoyl-sn-Glycero-3-phosphoethanolamine) is a preferred cargo lipid.

Intralipid may be comprised of the following composition: 1 000 mL contain: purified soybean oil 90 g, purified egg phospholipids 12 g, glycerol anhydrous 22 g, water for injection q.s. ad 1 000 mL. pH is adjusted with sodium hydroxide to pH approximately 8. Energy content/L: 4.6 MJ (190 kcal). Osmolality (approx.): 300 mOsm/kg water. In another embodiment fat emulsion is Liposyn that contains 5% safflower oil, 5% soybean oil, up to 1.2% egg phosphatides added as an emulsifier and 2.5% glycerin in water for injection. It may also contain sodium hydroxide for pH adjustment. pH 8.0 (6.0-9.0). Liposyn has an osmolarity of 276 m Osmol/liter (actual).

Variation in the identity, amounts and ratios of cargo lipids affects the cellular uptake and tissue distribution characteristics of these compounds. For example, the length of lipid tails and level of saturability will affect differential uptake to liver, lung, fat and cardiomyocytes. Addition of special hydrophobic molecules like vitamins or different forms of sterols can favor distribution to special tissues which are involved in the metabolism of particular compounds. Complexes are formed at different oligonucleotide concentrations, with higher concentrations favoring more efficient complex formation (FIGS. **21**-**22**).

In another embodiment, the fat emulsion is based on a mixture of lipids. Such lipids may include natural compounds, chemically synthesized compounds, purified fatty acids or any other lipids. In yet another embodiment the composition of fat emulsion is entirely artificial. In a particular embodiment, the fat emulsion is more then 70% linoleic acid. In yet another particular embodiment the fat emulsion is at least 1% of cardiolipin. Linoleic acid (LA) is an unsaturated omega-6 fatty acid. It is a colorless liquid made of a carboxylic acid with an 18-carbon chain and two cis double bonds.

In yet another embodiment of the present invention, the alteration of the composition of the fat emulsion is used as a way to alter tissue distribution of hydrophobicly modified polynucleotides. This methodology provides for the specific delivery of the polynucleotides to particular tissues (FIG. **12**).

In another embodiment the fat emulsions of the cargo molecule contain more then 70% of Linoleic acid ($C_{18}H_{32}O_2$) and/or cardiolipin are used for specifically delivering RNAi to heart muscle.

Fat emulsions, like intralipid have been used before as a delivery formulation for some non-water soluble drugs (such as Propofol, re-formulated as Diprivan). Unique features of the present invention include (a) the concept of combining modified polynucleotides with the hydrophobic compound(s), so it can be incorporated in the fat micelles and (b) mixing it with the fat emulsions to provide a reversible carrier. After injection into a blood stream, micelles usually bind to serum proteins, including albumin, HDL, LDL and other. This binding is reversible and eventually the fat is absorbed by cells. The polynucleotide, incorporated as a part of the micelle will then be delivered closely to the surface of the cells. After that cellular uptake might be happening though variable mechanisms, including but not limited to sterol type delivery.

Complexing Agents

Complexing agents bind to the oligonucleotides of the invention by a strong but non-covalent attraction (e.g., an electrostatic, van der Waals, pi-stacking, etc. interaction). In one embodiment, oligonucleotides of the invention can be complexed with a complexing agent to increase cellular uptake of oligonucleotides. An example of a complexing agent includes cationic lipids. Cationic lipids can be used to deliver oligonucleotides to cells. However, as discussed above, formulations free in cationic lipids are preferred in some embodiments.

The term "cationic lipid" includes lipids and synthetic lipids having both polar and non-polar domains and which are capable of being positively charged at or around physiological pH and which bind to polyanions, such as nucleic acids, and facilitate the delivery of nucleic acids into cells. In general cationic lipids include saturated and unsaturated alkyl and alicyclic ethers and esters of amines, amides, or derivatives thereof. Straight-chain and branched alkyl and alkenyl groups of cationic lipids can contain, e.g., from 1 to about 25 carbon atoms. Preferred straight chain or branched alkyl or alkene groups have six or more carbon atoms. Alicyclic groups include cholesterol and other steroid groups. Cationic lipids can be prepared with a variety of counterions (anions) including, e.g., Cl—, Br—, I—, F—, acetate, trifluoroacetate, sulfate, nitrite, and nitrate.

Examples of cationic lipids include polyethylenimine, polyamidoamine (PAMAM) starburst dendrimers, Lipofectin (a combination of DOTMA and DOPE), Lipofectase, LIPOFECTAMINE™ (e.g., LIPOFECTAMINE™ 2000), DOPE, Cytofectin (Gilead Sciences, Foster City, Calif.), and Eufectins (JBL, San Luis Obispo, Calif.). Exemplary cationic liposomes can be made from N-[1-(2,3-dioleoloxy)-propyl]-N,N,N-trimethylammonium chloride (DOTMA), N-[1-(2,3-

dioleoloxy)-propyl]-N,N,N-trimethylammonium methylsulfate (DOTAP), 3β-[N—(N',N'-dimethylaminoethane) carbamoyl]cholesterol (DC-Chol), 2,3,-dioleyloxy-N-[2 (sperminecarboxamido)ethyl]-N,N-dimethyl-1-propanaminium trifluoroacetate (DOSPA), 1,2-dimyristyloxypropyl-3-dimethyl-hydroxyethyl ammonium bromide; and dimethyldioctadecylammonium bromide (DDAB). The cationic lipid N-(1-(2,3-dioleyloxy)propyl)-N,N,N-trimethylammonium chloride (DOTMA), for example, was found to increase 1000-fold the antisense effect of a phosphorothioate oligonucleotide. (Vlassov et al., 1994, Biochimica et Biophysica Acta 1197:95-108). Oligonucleotides can also be complexed with, e.g., poly(L-lysine) or avidin and lipids may, or may not, be included in this mixture, e.g., steryl-poly(L-lysine).

Cationic lipids have been used in the art to deliver oligonucleotides to cells (see, e.g., U.S. Pat. Nos. 5,855,910; 5,851,548; 5,830,430; 5,780,053; 5,767,099; Lewis et al. 1996. *Proc. Natl. Acad. Sci. USA* 93:3176; Hope et al. 1998. *Molecular Membrane Biology* 15:1). Other lipid compositions which can be used to facilitate uptake of the instant oligonucleotides can be used in connection with the claimed methods. In addition to those listed supra, other lipid compositions are also known in the art and include, e.g., those taught in U.S. Pat. No. 4,235,871; U.S. Pat. Nos. 4,501,728; 4,837,028; 4,737,323.

In one embodiment lipid compositions can further comprise agents, e.g., viral proteins to enhance lipid-mediated transfections of oligonucleotides (Kamata, et al., 1994. *Nucl. Acids. Res.* 22:536). In another embodiment, oligonucleotides are contacted with cells as part of a composition comprising an oligonucleotide, a peptide, and a lipid as taught, e.g., in U.S. Pat. No. 5,736,392. Improved lipids have also been described which are serum resistant (Lewis, et al., 1996. *Proc. Natl. Acad. Sci.* 93:3176). Cationic lipids and other complexing agents act to increase the number of oligonucleotides carried into the cell through endocytosis.

In another embodiment N-substituted glycine oligonucleotides (peptoids) can be used to optimize uptake of oligonucleotides. Peptoids have been used to create cationic lipid-like compounds for transfection (Murphy, et al., 1998. *Proc. Natl. Acad. Sci.* 95:1517). Peptoids can be synthesized using standard methods (e.g., Zuckermann, R. N., et al. 1992. *J. Am. Chem. Soc.* 114:10646; Zuckermann, R. N., et al. 1992. *Int. J. Peptide Protein Res.* 40:497). Combinations of cationic lipids and peptoids, liptoids, can also be used to optimize uptake of the subject oligonucleotides (Hunag, et al., 1998. *Chemistry and Biology.* 5:345). Liptoids can be synthesized by elaborating peptoid oligonucleotides and coupling the amino terminal submonomer to a lipid via its amino group (Hunag, et al., 1998. *Chemistry and Biology.* 5:345).

It is known in the art that positively charged amino acids can be used for creating highly active cationic lipids (Lewis et al. 1996. *Proc. Natl. Acad. Sci. U.S.A.* 93:3176). In one embodiment, a composition for delivering oligonucleotides of the invention comprises a number of arginine, lysine, histidine or ornithine residues linked to a lipophilic moiety (see e.g., U.S. Pat. No. 5,777,153).

In another embodiment, a composition for delivering oligonucleotides of the invention comprises a peptide having from between about one to about four basic residues. These basic residues can be located, e.g., on the amino terminal, C-terminal, or internal region of the peptide. Families of amino acid residues having similar side chains have been defined in the art. These families include amino acids with basic side chains (e.g., lysine, arginine, histidine), acidic side chains (e.g., aspartic acid, glutamic acid), uncharged polar side chains (e.g., glycine (can also be considered non-polar), asparagine, glutamine, serine, threonine, tyrosine, cysteine), nonpolar side chains (e.g., alanine, valine, leucine, isoleucine, proline, phenylalanine, methionine, tryptophan), beta-branched side chains (e.g., threonine, valine, isoleucine) and aromatic side chains (e.g., tyrosine, phenylalanine, tryptophan, histidine). Apart from the basic amino acids, a majority or all of the other residues of the peptide can be selected from the non-basic amino acids, e.g., amino acids other than lysine, arginine, or histidine. Preferably a preponderance of neutral amino acids with long neutral side chains are used.

In one embodiment, a composition for delivering oligonucleotides of the invention comprises a natural or synthetic polypeptide having one or more gamma carboxyglutamic acid residues, or γ-Gla residues. These gamma carboxyglutamic acid residues may enable the polypeptide to bind to each other and to membrane surfaces. In other words, a polypeptide having a series of γ-Gla may be used as a general delivery modality that helps an RNAi construct to stick to whatever membrane to which it comes in contact. This may at least slow RNAi constructs from being cleared from the blood stream and enhance their chance of homing to the target.

The gamma carboxyglutamic acid residues may exist in natural proteins (for example, prothrombin has 10 γ-Gla residues). Alternatively, they can be introduced into the purified, recombinantly produced, or chemically synthesized polypeptides by carboxylation using, for example, a vitamin K-dependent carboxylase. The gamma carboxyglutamic acid residues may be consecutive or non-consecutive, and the total number and location of such gamma carboxyglutamic acid residues in the polypeptide can be regulated/fine tuned to achieve different levels of "stickiness" of the polypeptide.

In one embodiment, the cells to be contacted with an oligonucleotide composition of the invention are contacted with a mixture comprising the oligonucleotide and a mixture comprising a lipid, e.g., one of the lipids or lipid compositions described supra for between about 12 hours to about 24 hours. In another embodiment, the cells to be contacted with an oligonucleotide composition are contacted with a mixture comprising the oligonucleotide and a mixture comprising a lipid, e.g., one of the lipids or lipid compositions described supra for between about 1 and about five days. In one embodiment, the cells are contacted with a mixture comprising a lipid and the oligonucleotide for between about three days to as long as about 30 days. In another embodiment, a mixture comprising a lipid is left in contact with the cells for at least about five to about 20 days. In another embodiment, a mixture comprising a lipid is left in contact with the cells for at least about seven to about 15 days.

For example, in one embodiment, an oligonucleotide composition can be contacted with cells in the presence of a lipid such as cytofectin CS or GSV (available from Glen Research; Sterling, Va.), GS3815, GS2888 for prolonged incubation periods as described herein.

In one embodiment, the incubation of the cells with the mixture comprising a lipid and an oligonucleotide composition does not reduce the viability of the cells. Preferably, after the transfection period the cells are substantially viable. In one embodiment, after transfection, the cells are between at least about 70% and at least about 100% viable. In another embodiment, the cells are between at least about 80% and at least about 95% viable. In yet another embodiment, the cells are between at least about 85% and at least about 90% viable.

In one embodiment, oligonucleotides are modified by attaching a peptide sequence that transports the oligonucleotide into a cell, referred to herein as a "transporting peptide." In one embodiment, the composition includes an oligonucleotide which is complementary to a target nucleic acid molecule encoding the protein, and a covalently attached transporting peptide.

The language "transporting peptide" includes an amino acid sequence that facilitates the transport of an oligonucleotide into a cell. Exemplary peptides which facilitate the transport of the moieties to which they are linked into cells are known in the art, and include, e.g., HIV TAT transcription factor, lactoferrin, Herpes VP22 protein, and fibroblast growth factor 2 (Pooga et al. 1998. *Nature Biotechnology*. 16:857; and Derossi et al. 1998. *Trends in Cell Biology*. 8:84; Elliott and O'Hare. 1997. Cell 88:223).

Oligonucleotides can be attached to the transporting peptide using known techniques, e.g., (Prochiantz, A. 1996. *Curr. Opin. Neurobiol.* 6:629; Derossi et al. 1998. *Trends Cell Biol.* 8:84; Troy et al. 1996. *J. Neurosci.* 16:253), Vives et al. 1997. *J. Biol. Chem.* 272:16010). For example, in one embodiment, oligonucleotides bearing an activated thiol group are linked via that thiol group to a cysteine present in a transport peptide (e.g., to the cysteine present in the (3 turn between the second and the third helix of the antennapedia homeodomain as taught, e.g., in Derossi et al. 1998. *Trends Cell Biol.* 8:84; Prochiantz. 1996. *Current Opinion in Neurobiol.* 6:629; Allinquant et al. 1995. J. Cell Biol. 128:919). In another embodiment, a Boc-Cys-(Npys)OH group can be coupled to the transport peptide as the last (N-terminal) amino acid and an oligonucleotide bearing an SH group can be coupled to the peptide (Troy et al. 1996. *J. Neurosci.* 16:253).

In one embodiment, a linking group can be attached to a nucleomonomer and the transporting peptide can be covalently attached to the linker. In one embodiment, a linker can function as both an attachment site for a transporting peptide and can provide stability against nucleases. Examples of suitable linkers include substituted or unsubstituted C_1-C_{20} alkyl chains, C_2-C_{20} alkenyl chains, C_2-C_{20} alkynyl chains, peptides, and heteroatoms (e.g., S, O, NH, etc.). Other exemplary linkers include bifunctional crosslinking agents such as sulfosuccinimidyl-4-(maleimidophenyl)-butyrate (SMPB) (see, e.g., Smith et al. Biochem J 1991.276: 417-2).

In one embodiment, oligonucleotides of the invention are synthesized as molecular conjugates which utilize receptor-mediated endocytotic mechanisms for delivering genes into cells (see, e.g., Bunnell et al. 1992. *Somatic Cell and Molecular Genetics*. 18:559, and the references cited therein).

Targeting Agents

The delivery of oligonucleotides can also be improved by targeting the oligonucleotides to a cellular receptor. The targeting moieties can be conjugated to the oligonucleotides or attached to a carrier group (i.e., poly(L-lysine) or liposomes) linked to the oligonucleotides. This method is well suited to cells that display specific receptor-mediated endocytosis.

For instance, oligonucleotide conjugates to 6-phosphomannosylated proteins are internalized 20-fold more efficiently by cells expressing mannose 6-phosphate specific receptors than free oligonucleotides. The oligonucleotides may also be coupled to a ligand for a cellular receptor using a biodegradable linker. In another example, the delivery construct is mannosylated streptavidin which forms a tight complex with biotinylated oligonucleotides. Mannosylated streptavidin was found to increase 20-fold the internalization of biotinylated oligonucleotides. (Vlassov et al. 1994. *Biochimica et Biophysica Acta* 1197:95-108).

In addition specific ligands can be conjugated to the polylysine component of polylysine-based delivery systems. For example, transferrin-polylysine, adenovirus-polylysine, and influenza virus hemagglutinin HA-2 N-terminal fusogenic peptides-polylysine conjugates greatly enhance receptor-mediated DNA delivery in eucaryotic cells. Mannosylated glycoprotein conjugated to poly(L-lysine) in aveolar macrophages has been employed to enhance the cellular uptake of oligonucleotides. Liang et al. 1999. *Pharmazie* 54:559-566.

Because malignant cells have an increased need for essential nutrients such as folic acid and transferrin, these nutrients can be used to target oligonucleotides to cancerous cells. For example, when folic acid is linked to poly(L-lysine) enhanced oligonucleotide uptake is seen in promyelocytic leukaemia (HL-60) cells and human melanoma (M-14) cells. Ginobbi et al. 1997. *Anticancer Res.* 17:29. In another example, liposomes coated with maleylated bovine serum albumin, folic acid, or ferric protoporphyrin IX, show enhanced cellular uptake of oligonucleotides in murine macrophages, KB cells, and 2.2.15 human hepatoma cells. Liang et al. 1999. *Pharmazie* 54:559-566.

Liposomes naturally accumulate in the liver, spleen, and reticuloendothelial system (so-called, passive targeting). By coupling liposomes to various ligands such as antibodies are protein A, they can be actively targeted to specific cell populations. For example, protein A-bearing liposomes may be pretreated with H-2K specific antibodies which are targeted to the mouse major histocompatibility complex-encoded H-2K protein expressed on L cells. (Vlassov et al. 1994. *Biochimica et Biophysica Acta* 1197:95-108).

Other in vitro and/or in vivo delivery of RNAi reagents are known in the art, and can be used to deliver the subject RNAi constructs. See, for example, U.S. patent application publications 20080152661, 20080112916, 20080107694, 20080038296, 20070231392, 20060240093, 20060178327, 20060008910, 20050265957, 20050064595, 20050042227, 20050037496, 20050026286, 20040162235, 20040072785, 20040063654, 20030157030, WO 2008/036825, WO04/065601, and AU2004206255B2, just to name a few (all incorporated by reference).

Administration

The optimal course of administration or delivery of the oligonucleotides may vary depending upon the desired result and/or on the subject to be treated. As used herein "administration" refers to contacting cells with oligonucleotides and can be performed in vitro or in vivo. The dosage of oligonucleotides may be adjusted to optimally reduce expression of a protein translated from a target nucleic acid molecule, e.g., as measured by a readout of RNA stability or by a therapeutic response, without undue experimentation.

For example, expression of the protein encoded by the nucleic acid target can be measured to determine whether or not the dosage regimen needs to be adjusted accordingly. In addition, an increase or decrease in RNA or protein levels in a cell or produced by a cell can be measured using any art recognized technique. By determining whether transcription has been decreased, the effectiveness of the oligonucleotide in inducing the cleavage of a target RNA can be determined.

Any of the above-described oligonucleotide compositions can be used alone or in conjunction with a pharmaceutically acceptable carrier. As used herein, "pharmaceutically acceptable carrier" includes appropriate solvents, dispersion media, coatings, antibacterial and antifungal agents, isotonic and absorption delaying agents, and the like. The use of such media and agents for pharmaceutical active substances is well known in the art. Except insofar as any conventional media or agent is incompatible with the active ingredient, it can be used in the therapeutic compositions. Supplementary active ingredients can also be incorporated into the compositions.

Oligonucleotides may be incorporated into liposomes or liposomes modified with polyethylene glycol or admixed with cationic lipids for parenteral administration. Incorporation of additional substances into the liposome, for example, antibodies reactive against membrane proteins found on specific target cells, can help target the oligonucleotides to specific cell types.

Moreover, the present invention provides for administering the subject oligonucleotides with an osmotic pump providing continuous infusion of such oligonucleotides, for example, as described in Rataiczak et al. (1992 *Proc. Natl. Acad. Sci. USA* 89:11823-11827). Such osmotic pumps are commercially available, e.g., from Alzet Inc. (Palo Alto, Calif.). Topical administration and parenteral administration in a cationic lipid carrier are preferred.

With respect to in vivo applications, the formulations of the present invention can be administered to a patient in a variety of forms adapted to the chosen route of administration, e.g., parenterally, orally, or intraperitoneally. Parenteral administration, which is preferred, includes administration by the following routes: intravenous; intramuscular; interstitially; intraarterially; subcutaneous; intra ocular; intrasynovial; trans epithelial, including transdermal; pulmonary via inhalation; ophthalmic; sublingual and buccal; topically, including ophthalmic; dermal; ocular; rectal; and nasal inhalation via insufflation.

Pharmaceutical preparations for parenteral administration include aqueous solutions of the active compounds in water-soluble or water-dispersible form. In addition, suspensions of the active compounds as appropriate oily injection suspensions may be administered. Suitable lipophilic solvents or vehicles include fatty oils, for example, sesame oil, or synthetic fatty acid esters, for example, ethyl oleate or triglycerides. Aqueous injection suspensions may contain substances which increase the viscosity of the suspension include, for example, sodium carboxymethyl cellulose, sorbitol, or dextran, optionally, the suspension may also contain stabilizers. The oligonucleotides of the invention can be formulated in liquid solutions, preferably in physiologically compatible buffers such as Hank's solution or Ringer's solution. In addition, the oligonucleotides may be formulated in solid form and redissolved or suspended immediately prior to use. Lyophilized forms are also included in the invention.

Pharmaceutical preparations for topical administration include transdermal patches, ointments, lotions, creams, gels, drops, sprays, suppositories, liquids and powders. In addition, conventional pharmaceutical carriers, aqueous, powder or oily bases, or thickeners may be used in pharmaceutical preparations for topical administration.

Pharmaceutical preparations for oral administration include powders or granules, suspensions or solutions in water or non-aqueous media, capsules, sachets or tablets. In addition, thickeners, flavoring agents, diluents, emulsifiers, dispersing aids, or binders may be used in pharmaceutical preparations for oral administration.

For transmucosal or transdermal administration, penetrants appropriate to the barrier to be permeated are used in the formulation. Such penetrants are known in the art, and include, for example, for transmucosal administration bile salts and fusidic acid derivatives, and detergents. Transmucosal administration may be through nasal sprays or using suppositories. For oral administration, the oligonucleotides are formulated into conventional oral administration forms such as capsules, tablets, and tonics. For topical administration, the oligonucleotides of the invention are formulated into ointments, salves, gels, or creams as known in the art.

Drug delivery vehicles can be chosen e.g., for in vitro, for systemic, or for topical administration. These vehicles can be designed to serve as a slow release reservoir or to deliver their contents directly to the target cell. An advantage of using

some direct delivery drug vehicles is that multiple molecules are delivered per uptake. Such vehicles have been shown to increase the circulation half-life of drugs that would otherwise be rapidly cleared from the blood stream. Some examples of such specialized drug delivery vehicles which fall into this category are liposomes, hydrogels, cyclodextrins, biodegradable nanocapsules, and bioadhesive microspheres.

The described oligonucleotides may be administered systemically to a subject. Systemic absorption refers to the entry of drugs into the blood stream followed by distribution throughout the entire body. Administration routes which lead to systemic absorption include: intravenous, subcutaneous, intraperitoneal, and intranasal. Each of these administration routes delivers the oligonucleotide to accessible diseased cells. Following subcutaneous administration, the therapeutic agent drains into local lymph nodes and proceeds through the lymphatic network into the circulation. The rate of entry into the circulation has been shown to be a function of molecular weight or size. The use of a liposome or other drug carrier localizes the oligonucleotide at the lymph node. The oligonucleotide can be modified to diffuse into the cell, or the liposome can directly participate in the delivery of either the unmodified or modified oligonucleotide into the cell.

The chosen method of delivery will result in entry into cells. Preferred delivery methods include liposomes (10-400 nm), hydrogels, controlled-release polymers, and other pharmaceutically applicable vehicles, and microinjection or electroporation (for ex vivo treatments).

The pharmaceutical preparations of the present invention may be prepared and formulated as emulsions. Emulsions are usually heterogeneous systems of one liquid dispersed in another in the form of droplets usually exceeding 0.1 μm in diameter. The emulsions of the present invention may contain excipients such as emulsifiers, stabilizers, dyes, fats, oils, waxes, fatty acids, fatty alcohols, fatty esters, humectants, hydrophilic colloids, preservatives, and anti-oxidants may also be present in emulsions as needed. These excipients may be present as a solution in either the aqueous phase, oily phase or itself as a separate phase.

Examples of naturally occurring emulsifiers that may be used in emulsion formulations of the present invention include lanolin, beeswax, phosphatides, lecithin and acacia. Finely divided solids have also been used as good emulsifiers especially in combination with surfactants and in viscous preparations. Examples of finely divided solids that may be used as emulsifiers include polar inorganic solids, such as heavy metal hydroxides, nonswelling clays such as bentonite, attapulgite, hectorite, kaolin, montrnorillonite, colloidal aluminum silicate and colloidal magnesium aluminum silicate, pigments and nonpolar solids such as carbon or glyceryl tristearate.

Examples of preservatives that may be included in the emulsion formulations include methyl paraben, propyl paraben, quaternary ammonium salts, benzalkonium chloride, esters of p-hydroxybenzoic acid, and boric acid. Examples of antioxidants that may be included in the emulsion formulations include free radical scavengers such as tocopherols, alkyl gallates, butylated hydroxyanisole, butylated hydroxytoluene, or reducing agents such as ascorbic acid and sodium metabisulfite, and antioxidant synergists such as citric acid, tartaric acid, and lecithin.

In one embodiment, the compositions of oligonucleotides are formulated as microemulsions. A microemulsion is a system of water, oil and amphiphile which is a single optically isotropic and thermodynamically stable liquid solution. Typically microemulsions are prepared by first dispersing an oil in an aqueous surfactant solution and then adding a sufficient amount of a 4th component, generally an intermediate chain-length alcohol to form a transparent system.

Surfactants that may be used in the preparation of microemulsions include, but are not limited to, ionic surfactants, non-ionic surfactants, Brij 96, polyoxyethylene oleyl ethers, polyglycerol fatty acid esters, tetraglycerol monolaurate (ML310), tetraglycerol monooleate (MO310), hexaglycerol monooleate (PO310), hexaglycerol pentaoleate (PO500), decaglycerol monocaprate (MCA750), decaglycerol monooleate (MO750), decaglycerol sequioleate (S0750), decaglycerol decaoleate (DA0750), alone or in combination with cosurfactants. The cosurfactant, usually a short-chain alcohol such as ethanol, 1-propanol, and 1-butanol, serves to increase the interfacial fluidity by penetrating into the surfactant film and consequently creating a disordered film because of the void space generated among surfactant molecules.

Microemulsions may, however, be prepared without the use of cosurfactants and alcohol-free self-emulsifying microemulsion systems are known in the art. The aqueous phase may typically be, but is not limited to, water, an aqueous solution of the drug, glycerol, PEG300, PEG400, polyglycerols, propylene glycols, and derivatives of ethylene glycol. The oil phase may include, but is not limited to, materials such as Captex 300, Captex 355, Capmul MCM, fatty acid esters, medium chain (C_8-C_{12}) mono, di, and tri-glycerides, polyoxyethylated glyceryl fatty acid esters, fatty alcohols, polyglycolized glycerides, saturated polyglycolized C_8-C_{10} glycerides, vegetable oils and silicone oil.

Microemulsions are particularly of interest from the standpoint of drug solubilization and the enhanced absorption of drugs. Lipid based microemulsions (both oil/water and water/oil) have been proposed to enhance the oral bioavailability of drugs.

Microemulsions offer improved drug solubilization, protection of drug from enzymatic hydrolysis, possible enhancement of drug absorption due to surfactant-induced alterations in membrane fluidity and permeability, ease of preparation, ease of oral administration over solid dosage forms, improved clinical potency, and decreased toxicity (Constantinides et al., Pharmaceutical Research, 1994, 11:1385; Ho et al., J. Pharm. Sci., 1996, 85:138-143). Microemulsions have also been effective in the transdermal delivery of active components in both cosmetic and pharmaceutical applications. It is expected that the microemulsion compositions and formulations of the present invention will facilitate the increased systemic absorption of oligonucleotides from the gastrointestinal tract, as well as improve the local cellular uptake of oligonucleotides within the gastrointestinal tract, vagina, buccal cavity and other areas of administration.

In an embodiment, the present invention employs various penetration enhancers to affect the efficient delivery of nucleic acids, particularly oligonucleotides, to the skin of animals. Even non-lipophilic drugs may cross cell membranes if the membrane to be crossed is treated with a penetration enhancer. In addition to increasing the diffusion of non-lipophilic drugs across cell membranes, penetration enhancers also act to enhance the permeability of lipophilic drugs.

Five categories of penetration enhancers that may be used in the present invention include: surfactants, fatty acids, bile salts, chelating agents, and non-chelating non-surfactants. Other agents may be utilized to enhance the penetration of the administered oligonucleotides include: glycols such as ethylene glycol and propylene glycol, pyrrols such as 2-15 pyrrol, azones, and terpenes such as limonene, and menthone.

The oligonucleotides, especially in lipid formulations, can also be administered by coating a medical device, for example, a catheter, such as an angioplasty balloon catheter, with a cationic lipid formulation. Coating may be achieved, for example, by dipping the medical device into a lipid formulation or a mixture of a lipid formulation and a suitable solvent, for example, an aqueous-based buffer, an aqueous solvent, ethanol, methylene chloride, chloroform and the like. An amount of the formulation will naturally adhere to the surface of the device which is subsequently administered to a patient, as appropriate. Alternatively, a lyophilized mixture of a lipid formulation may be specifically bound to the surface of the device. Such binding techniques are described, for example, in K. Ishihara et al., Journal of Biomedical Materials Research, Vol. 27, pp. 1309-1314 (1993), the disclosures of which are incorporated herein by reference in their entirety.

The useful dosage to be administered and the particular mode of administration will vary depending upon such factors as the cell type, or for in vivo use, the age, weight and the particular animal and region thereof to be treated, the particular oligonucleotide and delivery method used, the therapeutic or diagnostic use contemplated, and the form of the formulation, for example, suspension, emulsion, micelle or liposome, as will be readily apparent to those skilled in the art. Typically, dosage is administered at lower levels and increased until the desired effect is achieved. When lipids are used to deliver the oligonucleotides, the amount of lipid compound that is administered can vary and generally depends upon the amount of oligonucleotide agent being administered. For example, the weight ratio of lipid compound to oligonucleotide agent is preferably from about 1:1 to about 15:1, with a weight ratio of about 5:1 to about 10:1 being more preferred. Generally, the amount of cationic lipid compound which is administered will vary from between about 0.1 milligram (mg) to about 1 gram (g). By way of general guidance, typically between about 0.1 mg and about 10 mg of the particular oligonucleotide agent, and about 1 mg to about 100 mg of the lipid compositions, each per kilogram of patient body weight, is administered, although higher and lower amounts can be used.

The agents of the invention are administered to subjects or contacted with cells in a biologically compatible form suitable for pharmaceutical administration. By "biologically compatible form suitable for administration" is meant that the oligonucleotide is administered in a form in which any toxic effects are outweighed by the therapeutic effects of the oligonucleotide. In one embodiment, oligonucleotides can be administered to subjects. Examples of subjects include mammals, e.g., humans and other primates; cows, pigs, horses, and farming (agricultural) animals; dogs, cats, and other domesticated pets; mice, rats, and transgenic non-human animals.

Administration of an active amount of an oligonucleotide of the present invention is defined as an amount effective, at dosages and for periods of time necessary to achieve the desired result. For example, an active amount of an oligonucleotide may vary according to factors such as the type of cell, the oligonucleotide used, and for in vivo uses the disease state, age, sex, and weight of the individual, and the ability of the oligonucleotide to elicit a desired response in the individual. Establishment of therapeutic levels of oligonucleotides within the cell is dependent upon the rates of uptake and efflux or degradation. Decreasing the degree of degradation prolongs the intracellular half-life of the oligonucleotide. Thus, chemically-modified oligonucleotides, e.g., with modification of the phosphate backbone, may require different dosing.

The exact dosage of an oligonucleotide and number of doses administered will depend upon the data generated experimentally and in clinical trials. Several factors such as the desired effect, the delivery vehicle, disease indication, and the route of administration, will affect the dosage. Dosages can be readily determined by one of ordinary skill in the art and formulated into the subject pharmaceutical compositions. Preferably, the duration of treatment will extend at least through the course of the disease symptoms.

Dosage regim may be adjusted to provide the optimum therapeutic response. For example, the oligonucleotide may be repeatedly administered, e.g., several doses may be administered daily or the dose may be proportionally reduced as indicated by the exigencies of the therapeutic situation. One of ordinary skill in the art will readily be able to determine appropriate doses and schedules of administration of the subject oligonucleotides, whether the oligonucleotides are to be administered to cells or to subjects.

Physical methods of introducing nucleic acids include injection of a solution containing the nucleic acid, bombardment by particles covered by the nucleic acid, soaking the cell or organism in a solution of the nucleic acid, or electroporation of cell membranes in the presence of the nucleic acid. A viral construct packaged into a viral particle would accomplish both efficient introduction of an expression construct into the cell and transcription of nucleic acid encoded by the expression construct. Other methods known in the art for introducing nucleic acids to cells may be used, such as lipid-mediated carrier transport, chemical-mediated transport, such as calcium phosphate, and the like. Thus the nucleic acid may be introduced along with components that perform one or more of the following activities: enhance nucleic acid uptake by the cell, inhibit annealing of single strands, stabilize the single strands, or other-wise increase inhibition of the target gene.

Nucleic acid may be directly introduced into the cell (i.e., intracellularly); or introduced extracellularly into a cavity, interstitial space, into the circulation of an organism, introduced orally or by inhalation, or may be introduced by bathing a cell or organism in a solution containing the nucleic acid. Vascular or extravascular circulation, the blood or lymph system, and the cerebrospinal fluid are sites where the nucleic acid may be introduced.

The cell with the target gene may be derived from or contained in any organism. The organism may a plant, animal, protozoan, bacterium, virus, or fungus. The plant may be a monocot, dicot or gymnosperm; the animal may be a vertebrate or invertebrate. Preferred microbes are those used in agriculture or by industry, and those that are pathogenic for plants or animals.

Alternatively, vectors, e.g., transgenes encoding a siRNA of the invention can be engineered into a host cell or transgenic animal using art recognized techniques.

Another use for the nucleic acids of the present invention (or vectors or transgenes encoding same) is a functional analysis to be carried out in eukaryotic cells, or eukaryotic non-human organisms, preferably mammalian cells or organisms and most preferably human cells, e.g. cell lines such as HeLa or 293 or rodents, e.g. rats and mice. By administering a suitable nucleic acid of the invention which is sufficiently complementary to a target mRNA sequence to direct target-specific RNA interference, a specific knockout or knockdown phenotype can be obtained in a target cell, e.g. in cell culture or in a target organism.

Thus, a further subject matter of the invention is a eukaryotic cell or a eukaryotic non-human organism exhibiting a target gene-specific knockout or knockdown phenotype comprising a fully or at least partially deficient expression of at least one endogenous target gene wherein said cell or organism is transfected with at least one vector comprising DNA encoding an RNAi agent capable of inhibiting the expression of the target gene. It should be noted that the present invention allows a target-specific knockout or knockdown of several different endogenous genes due to the specificity of the RNAi agent.

Gene-specific knockout or knockdown phenotypes of cells or non-human organisms, particularly of human cells or non-human mammals may be used in analytic to procedures, e.g. in the functional and/or phenotypical analysis of complex physiological processes such as analysis of gene expression profiles and/or proteomes. Preferably the analysis is carried out by high throughput methods using oligonucleotide based chips.

Assays of Oligonucleotide Stability

In some embodiments, the oligonucleotides of the invention are stabilized, i.e., substantially resistant to endonuclease and exonuclease degradation. An oligonucleotide is defined as being substantially resistant to nucleases when it is at least about 3-fold more resistant to attack by an endogenous cellular nuclease, and is highly nuclease resistant when it is at least about 6-fold more resistant than a corresponding oligonucleotide. This can be demonstrated by showing that the oligonucleotides of the invention are substantially resistant to nucleases using techniques which are known in the art.

One way in which substantial stability can be demonstrated is by showing that the oligonucleotides of the invention function when delivered to a cell, e.g., that they reduce transcription or translation of target nucleic acid molecules, e.g., by measuring protein levels or by measuring cleavage of mRNA. Assays which measure the stability of target RNA can be performed at about 24 hours post-transfection (e.g., using Northern blot techniques, RNase Protection Assays, or QC-PCR assays as known in the art). Alternatively, levels of the target protein can be measured. Preferably, in addition to testing the RNA or protein levels of interest, the RNA or protein levels of a control, non-targeted gene will be measured (e.g., actin, or preferably a control with sequence similarity to the target) as a specificity control. RNA or protein measurements can be made using any art-recognized technique. Preferably, measurements will be made beginning at about 16-24 hours post transfection. (M. Y. Chiang, et al. 1991. J Biol Chem. 266:18162-71; T. Fisher, et al. 1993. Nucleic Acids Research. 21 3857).

The ability of an oligonucleotide composition of the invention to inhibit protein synthesis can be measured using techniques which are known in the art, for example, by detecting an inhibition in gene transcription or protein synthesis. For example, Nuclease Si mapping can be performed. In another example, Northern blot analysis can be used to measure the presence of RNA encoding a particular protein. For example, total RNA can be prepared over a cesium chloride cushion (see, e.g., Ausebel et al., 1987. Current Protocols in Molecular Biology (Greene & Wiley, New York)). Northern blots can then be made using the RNA and probed (see, e.g., Id.). In another example, the level of the specific mRNA produced by the target protein can be measured, e.g., using PCR. In yet another example, Western blots can be used to measure the amount of target protein present. In still another embodiment, a phenotype influenced by the amount of the protein can be detected. Techniques for performing Western blots are well known in the art, see, e.g., Chen et al. J. Biol. Chem. 271: 28259.

In another example, the promoter sequence of a target gene can be linked to a reporter gene and reporter gene transcription (e.g., as described in more detail below) can be monitored. Alternatively, oligonucleotide compositions that do not target a promoter can be identified by fusing a portion of the target nucleic acid molecule with a reporter gene so that the reporter gene is transcribed. By monitoring a change in the expression of the reporter gene in the presence of the oligonucleotide composition, it is possible to determine the effectiveness of the oligonucleotide composition in inhibiting the expression of the reporter gene. For example, in one embodiment, an effective oligonucleotide composition will reduce the expression of the reporter gene.

A "reporter gene" is a nucleic acid that expresses a detectable gene product, which may be RNA or protein. Detection of mRNA expression may be accomplished by Northern blotting and detection of protein may be accomplished by staining with antibodies specific to the protein. Preferred reporter genes produce a readily detectable product. A reporter gene may be operably linked with a regulatory DNA sequence such that detection of the reporter gene product provides a measure of the transcriptional activity of the regulatory sequence. In preferred embodiments, the gene product of the reporter gene is detected by an intrinsic activity associated with that product. For instance, the reporter gene may encode a gene product that, by enzymatic activity, gives rise to a detectable signal based on color, fluorescence, or luminescence. Examples of reporter genes include, but are not limited to, those coding for chloramphenicol acetyl transferase (CAT), luciferase, beta-galactosidase, and alkaline phosphatase.

One skilled in the art would readily recognize numerous reporter genes suitable for use in the present invention. These include, but are not limited to, chloramphenicol acetyltransferase (CAT), luciferase, human growth hormone (hGH), and beta-galactosidase. Examples of such reporter genes can be found in F. A. Ausubel et al., Eds., Current Protocols in Molecular Biology, John Wiley & Sons, New York, (1989). Any gene that encodes a detectable product, e.g., any product having detectable enzymatic activity or against which a specific antibody can be raised, can be used as a reporter gene in the present methods.

One reporter gene system is the firefly luciferase reporter system. (Gould, S. J., and Subramani, S. 1988. Anal. Biochem., 7:404-408 incorporated herein by reference). The luciferase assay is fast and sensitive. In this assay, a lysate of the test cell is prepared and combined with ATP and the substrate luciferin. The encoded enzyme luciferase catalyzes a rapid, ATP dependent oxidation of the substrate to generate a light-emitting product. The total light output is measured and is proportional to the amount of luciferase present over a wide range of enzyme concentrations.

CAT is another frequently used reporter gene system; a major advantage of this system is that it has been an extensively validated and is widely accepted as a measure of promoter activity. (Gorman C. M., Moffat, L. F., and Howard, B. H. 1982. Mol. Cell. Biol., 2:1044-1051). In this system, test cells are transfected with CAT expression vectors and incubated with the candidate substance within 2-3 days of the initial transfection. Thereafter, cell extracts are prepared. The extracts are incubated with acetyl CoA and radioactive chloramphenicol. Following the incubation, acetylated chloramphenicol is separated from nonacetylated form by thin layer chromatography. In this assay, the degree of acetylation reflects the CAT gene activity with the particular promoter.

Another suitable reporter gene system is based on immunologic detection of hGH. This system is also quick and easy to use. (Selden, R., Burke-Howie, K. Rowe, M. E., Goodman, H. M., and Moore, D. D. (1986), Mol. Cell, Biol., 6:3173-3179 incorporated herein by reference). The hGH system is advantageous in that the expressed hGH polypeptide is assayed in the media, rather than in a cell extract. Thus, this system does not require the destruction of the test cells. It will be appreciated that the principle of this reporter gene system is not limited to hGH but rather adapted for use with any polypeptide for which an antibody of acceptable specificity is available or can be prepared.

In one embodiment, nuclease stability of a double-stranded oligonucleotide of the invention is measured and compared to a control, e.g., an RNAi molecule typically used in the art (e.g., a duplex oligonucleotide of less than 25 nucleotides in length and comprising 2 nucleotide base overhangs) or an unmodified RNA duplex with blunt ends.

The target RNA cleavage reaction achieved using the siRNAs of the invention is highly sequence specific. Sequence identity may determined by sequence comparison and alignment algorithms known in the art. To determine the percent identity of two nucleic acid sequences (or of two amino acid sequences), the sequences are aligned for optimal comparison purposes (e.g., gaps can be introduced in the first sequence or second sequence for optimal alignment). A preferred, non-limiting example of a local alignment algorithm utilized for the comparison of sequences is the algorithm of Karlin and Altschul (1990) Proc. Natl. Acad. Sci. USA 87:2264-68, modified as in Karlin and Altschul (1993) Proc. Natl. Acad. Sci. USA 90:5873-77. Such an algorithm is incorporated into the BLAST programs (version 2.0) of Altschul, et al. (1990) J. Mol. Biol. 215:403-10. Additionally, numerous commercial entities, such as Dharmacon, and Invitrogen provide access to algorithms on their website. The Whitehead Institute also offers a free siRNA Selection Program. Greater than 90% sequence identity, e.g., 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99% or even 100% sequence identity, between the siRNA and the portion of the target gene is preferred. Alternatively, the siRNA may be defined functionally as a nucleotide sequence (or oligonucleotide sequence) that is capable of hybridizing with a portion of the target gene transcript. Examples of stringency conditions for polynucleotide hybridization are provided in Sambrook, J., E. F. Fritsch, and T. Maniatis, 1989, Molecular Cloning: A Laboratory Manual, Cold Spring Harbor Laboratory Press, Cold Spring Harbor, N.Y., chapters 9 and 11, and Current Protocols in Molecular Biology, 1995, F. M. Ausubel et al., eds., John Wiley & Sons, Inc., sections 2.10 and 6.3-6.4, incorporated herein by reference.

Therapeutic Use

By inhibiting the expression of a gene, the oligonucleotide compositions of the present invention can be used to treat any disease involving the expression of a protein. Examples of diseases that can be treated by oligonucleotide compositions, just to illustrate, include: cancer, retinopathies, autoimmune diseases, inflammatory diseases (i.e., ICAM-1 related disorders, Psoriasis, Ulcerative Colitus, Crohn's disease), viral diseases (i.e., HIV, Hepatitis C), miRNA disorders, and cardiovascular diseases.

In one embodiment, in vitro treatment of cells with oligonucleotides can be used for ex vivo therapy of cells removed from a subject (e.g., for treatment of leukemia or viral infection) or for treatment of cells which did not originate in the subject, but are to be administered to the subject (e.g., to eliminate transplantation antigen expression on cells to be transplanted into a subject). In addition, in vitro treatment of cells can be used in non-therapeutic settings, e.g., to evaluate gene function, to study gene regulation and protein synthesis or to evaluate improvements made to oligonucleotides designed to modulate gene expression or protein synthesis. In vivo treatment of cells can be useful in certain clinical settings where it is desirable to inhibit the expression of a protein. There are numerous medical conditions for which antisense therapy is reported to be suitable (see, e.g., U.S. Pat. No. 5,830,653) as well as respiratory syncytial virus infection (WO 95/22,553) influenza virus (WO 94/23,028), and malignancies (WO 94/08,003). Other examples of clinical uses of antisense sequences are reviewed, e.g., in Glaser. 1996. *Genetic Engineering News* 16:1. Exemplary targets for cleavage by oligonucleotides include, e.g., protein kinase Ca, ICAM-1, c-raf kinase, p53, c-myb, and the bcr/abl fusion gene found in chronic myelogenous leukemia.

The subject nucleic acids can be used in RNAi-based therapy in any animal having RNAi pathway, such as human, non-human primate, non-human mammal, non-human vertebrates, rodents (mice, rats, hamsters, rabbits, etc.), domestic livestock animals, pets (cats, dogs, etc.), *Xenopus*, fish, insects (Drosophila, etc.), and worms (*C. elegans*), etc.

The invention provides methods for inhibiting or preventing in a subject, a disease or condition associated with an aberrant or unwanted target gene expression or activity, by administering to the subject a nucleic acid of the invention. If appropriate, subjects are first treated with a priming agent so as to be more responsive to the subsequent RNAi therapy. Subjects at risk for a disease which is caused or contributed to by aberrant or unwanted target gene expression or activity can be identified by, for example, any or a combination of diagnostic or prognostic assays known in the art. Administration of a prophylactic agent can occur prior to the manifestation of symptoms characteristic of the target gene aberrancy, such that a disease or disorder is prevented or, alternatively, delayed in its progression. Depending on the type of target gene aberrancy, for example, a target gene, target gene agonist or target gene antagonist agent can be used for treating the subject.

In another aspect, the invention pertains to methods of modulating target gene expression, protein expression or activity for therapeutic purposes. Accordingly, in an exemplary embodiment, the methods of the invention involve contacting a cell capable of expressing target gene with a nucleic acid of the invention that is specific for the target gene or protein (e.g., is specific for the mRNA encoded by said gene or specifying the amino acid sequence of said protein) such that expression or one or more of the activities of target protein is modulated. These methods can be performed in vitro (e.g., by culturing the cell with the agent), in vivo (e.g., by administering the agent to a subject), or ex vivo. The subjects may be first treated with a priming agent so as to be more responsive to the subsequent RNAi therapy if desired. As such, the present invention provides methods of treating a subject afflicted with a disease or disorder characterized by aberrant or unwanted expression or activity of a target gene polypeptide or nucleic acid molecule. Inhibition of target gene activity is desirable in situations in which target gene is abnormally unregulated and/or in which decreased target gene activity is likely to have a beneficial effect.

Thus the therapeutic agents of the invention can be administered to subjects to treat (prophylactically or therapeutically) disorders associated with aberrant or unwanted target gene activity. In conjunction with such treatment, pharmacogenomics (i.e., the study of the relationship between an individual's genotype and that individual's response to a foreign compound or drug) may be considered. Differences in metabolism of therapeutics can lead to severe toxicity or therapeutic failure by altering the relation between dose and blood concentration of the pharmacologically active drug. Thus, a physician or clinician may consider applying knowledge obtained in relevant pharmacogenomics studies in determining whether to administer a therapeutic agent as well as tailoring the dosage and/or therapeutic regimen of treatment with a therapeutic agent. Pharmacogenomics deals with clinically significant hereditary variations in the response to drugs due to altered drug disposition and abnormal action in affected persons.

For the purposes of the invention, ranges may be expressed herein as from "about" one particular value, and/or to "about" another particular value. When such a range is expressed, another embodiment includes from the one particular value and/or to the other particular value. Similarly, when values are expressed as approximations, by use of the antecedent "about," it will be understood that the particular value forms another embodiment. It will be further understood that the endpoints of each of the ranges are significant both in relation to the other endpoint, and independently of the other endpoint.

Moreover, for the purposes of the present invention, the term "a" or "an" entity refers to one or more of that entity; for example, "a protein" or "a nucleic acid molecule" refers to one or more of those compounds or at least one compound. As such, the terms "a" (or "an"), "one or more" and "at least one" can be used interchangeably herein. It is also to be noted that the terms "comprising", "including", and "having" can be used interchangeably. Furthermore, a compound "selected from the group consisting of" refers to one or more of the compounds in the list that follows, including mixtures (i.e., combinations) of two or more of the compounds. According to the present invention, an isolated, or biologically pure, protein or nucleic acid molecule is a compound that has been removed from its natural milieu. As such, "isolated" and "biologically pure" do not necessarily reflect the extent to which the compound has been purified. An isolated compound of the present invention can be obtained from its natural source, can be produced using molecular biology techniques or can be produced by chemical synthesis.

The present invention is further illustrated by the following Examples, which in no way should be construed as further limiting. The entire contents of all of the references (including literature references, issued patents, published patent applications, and co-pending patent applications) cited throughout this application are hereby expressly incorporated by reference.

EXAMPLES

Example 1

Inhibition of Gene Expression Using Minimum Length Trigger RNAs

Transfection of Minimum Length Trigger (mlt) RNA

mltRNA constructs were chemically synthesized (Integrated DNA Technologies, Coralville, Iowa) and transfected into HEK293 cells (ATCC, Manassas, Va.) using the Lipofectamine RNAiMAX (Invitrogen, Carlsbad, Calif.) reagent according to manufacturer's instructions. In brief, RNA was diluted to a 12× concentration and then combined with a 12× concentration of Lipofectamine RNAiMAX to complex. The RNA and transfection reagent were allowed to complex at room temperature for 20 minutes and make a 6× concentration. While complexing, HEK293 cells were washed, trypsinized and counted. The cells were diluted to a concentration recommended by the manufacturer and previously described conditions which was at 1×10^5 cells/ml. When RNA had completed complexing with the RNAiMAX transfection reagent, 20 ul of the complexes were added to the appropriate well of the 96-well plate in triplicate. Cells were added to each well (100 ul volume) to make the final cell count per well at 1×10^4 cells/well. The volume of cells diluted the 6× concentration of complex to 1× which was equal to a concentration noted (between 10-0.05 nM). Cells were incubated for 24 or 48 hours under normal growth conditions.

After 24 or 48 hour incubation cells were lysed and gene silencing activity was measured using the QuantiGene assay (Panomics, Freemont, Calif.) which employs bDNA hybridization technology. The assay was carried out according to manufacturer's instructions.

ΔG Calculation

ΔG was calculated using Mfold, available through the Mfold internet site (http://mfold.bioinfo.rpi.edu/cgi-bin/rna-form1.cgi). Methods for calculating ΔG are described in, and are incorporated by reference from, the following references: Zuker, M. (2003) Nucleic Acids Res., 31(13):3406-15; Mathews, D. H., Sabina, J., Zuker, M. and Turner, D. H. (1999) J. Mol. Biol. 288:911-940; Mathews, D. H., Disney, M. D., Childs, J. L., Schroeder, S. J., Zuker, M., and Turner, D. H. (2004) Proc. Natl. Acad. Sci. 101:7287-7292; Duan, S., Mathews, D. H., and Turner, D. H. (2006) Biochemistry 45:9819-9832; Wuchty, S., Fontana, W., Hofacker, I. L., and Schuster, P. (1999) Biopolymers 49:145-165.

Example 2

Optimization of sd-rxRNA^{nano} Molecules for Gene Silencing

Asymmetric double stranded RNAi molecules, with minimal double stranded regions, were developed herein and are highly effective at gene silencing. These molecules can contain a variety of chemical modifications on the sense and/or anti-sense strands, and can be conjugated to sterol-like compounds such as cholesterol.

FIGS. **1-3** present schematics of RNAi molecules associated with the invention. In the asymmetric molecules, which contain a sense and anti-sense strand, either of the strands can be the longer strand. Either strand can also contain a single-stranded region. There can also be mismatches between the sense and anti-sense strand, as indicated in FIG. **1**D. Preferably, one end of the double-stranded molecule is either blunt-ended or contains a short overhang such as an overhang of one nucleotide. FIG. **2** indicates types of chemical modifications applied to the sense and anti-sense strands including 2'F, 2'OMe, hydrophobic modifications and phosphorothioate modifications. Preferably, the single stranded region of the molecule contains multiple phosphorothioate modifications. Hydrophobicity of molecules can be increased using such compounds as 4-pyridyl at 5-U, 2-pyridyl at 5-U, isobutyl at 5-U and indolyl at 5-U (FIG. **2**). Proteins or peptides such as protamine (or other Arg rich peptides), spermidine or other similar chemical structures can also be used to block duplex charge and facilitate cellular entry (FIG. **3**). Increased hydrophobicity can be achieved through either covalent or non-covalent modifications. Several positively charged chemicals, which might be used for polynucleotide charge blockage are depicted in FIG. **4**.

Chemical modifications of polynucleotides, such as the guide strand in a duplex molecule, can facilitate RISC entry. FIG. **5** depicts single stranded polynucleotides, representing a guide strand in a duplex molecule, with a variety of chemical modifications including 2' d, 2'OMe, 2'F, hydrophobic modifications, phosphorothioate modifications, and attachment of conjugates such as "X" in FIG. **5**, where X can be a small molecule with high affinity to a PAZ domain, or sterol-type entity. Similarly, FIG. **6** depicts single stranded polynucleotides, representing a passenger strand in a duplex molecule, with proposed structural and chemical compositions of RISC substrate inhibitors. Combinations of chemical modifications can ensure efficient uptake and efficient binding to preloaded RISC complexes.

FIG. **7** depicts structures of polynucleotides with sterol-type molecules attached, where R represents a polycarbonic tail of 9 carbons or longer. FIG. **8** presents examples of naturally occurring phytosterols with a polycarbon chain longer than 8 attached at position 17. More than 250 different types of phytosterols are known. FIG. **9** presents examples of sterol-like structures with variations in the sizes of the polycarbon chains attached at position 17. FIG. **91** presents further examples of sterol-type molecules that can be used as a hydrophobic entity in place of cholesterol. FIG. **92** presents further examples of hydrophobic molecules that might be used as hydrophobic entities in place of cholestesterol. Optimization of such characteristics can improve uptake properties of the RNAi molecules. FIG. **10** presents data adapted from Martins et al. (J Lipid Research), showing that the percentage of liver uptake and plasma clearance of lipid emulsions containing sterol-type molecules is directly affected by the size of the attached polycarbon chain at position 17. FIG. **11** depicts a micelle formed from a mixture of polynucleotides attached to hydrophobic conjugates and fatty acids. FIG. **12** describes how alteration in lipid composition can affect pharmacokinetic behavior and tissue distribution of hydrophobically modified and/or hydrophobically conjugated polynucleotides. In particular, the use of lipid mixtures that are enriched in linoleic acid and cardiolipin results in preferential uptake by cardiomyocites.

FIG. **13** depicts examples of RNAi constructs and controls designed to target MAP4K4 expression. FIGS. **14** and **15** reveal that RNAi constructs with minimal duplex regions (such as duplex regions of approximately 13 nucleotides) are effective in mediating RNA silencing in cell culture. Parameters associated with these RNA molecules are shown in FIG. **16**. FIG. **17** depicts examples of RNAi constructs and controls designed to target SOD1 expression. FIGS. **18** and **19** reveal the results of gene silencing experiments using these RNAi molecules to target SOD1 in cells. FIG. **20** presents a schematic indicating that RNA molecules with double stranded regions that are less than 10 nucleotides are not cleaved by Dicer, and FIG. **21** presents a schematic of a hypothetical RNAi model for RNA induced gene silencing.

The RNA molecules described herein were subject to a variety of chemical modifications on the sense and antisense strands, and the effects of such modifications were observed. RNAi molecules were synthesized and optimized through testing of a variety of modifications. In first generation optimization, the sense (passenger) and anti-sense (guide) strands of the sd-rxRNA^{nano} molecules were modified for example through incorporation of C and U 2'OMe modifications, 2'F modifications, phosphorothioate modifications, phosphorylation, and conjugation of cholesterol. Molecules were tested for inhibition of MAP4K4 expression in cells including HeLa, primary mouse hepatocytes and primary human hepatocytes through both lipid-mediated and passive uptake transfection.

FIG. **22** reveals that chemical modifications can enhance gene silencing. In particular, modifying the guide strand with 2'F UC modifications, and with a stretch of phosphorothioate modifications, combined with complete CU O'Me modification of the passenger strands, resulted in molecules that were highly effective in gene silencing. The effect of chemical modification on in vitro efficacy in un-assisted delivery in HeLa cells was also examined. FIG. **23** reveals that compounds lacking any of 2'F, 2'OMe, a stretch of phosphorothioate modifications, or cholesterol conjugates, were completely inactive in passive uptake. A combination of all 4 types of chemical modifications, for example in compound 12386, was found to be highly effective in gene silencing. FIG. **24** also shows the effectiveness of compound 12386 in gene silencing.

Optimization of the length of the oligonucleotide was also investigated. FIGS. **25** and **26** reveal that oligonucleotides with a length of 21 nucleotides were more effective than oligonucleotides with a length of 25 nucleotides, indicating that reduction in the size of an RNA molecule can improve efficiency, potentially by assisting in its uptake. Screening was also conducted to optimize the size of the duplex region of double stranded RNA molecules. FIG. **88** reveals that compounds with duplexes of 10 nucleotides were effective in inducing gene silencing. Positioning of the sense strand relative to the guide strand can also be critical for silencing gene expression (FIG. **89**). In this assay, a blunt end was found to be most effective. 3' overhangs were tolerated, but 5' overhangs resulted in a complete loss of functionality. The guide strand can be effective in gene silencing when hybridized to a sense strand of varying lengths (FIG. **90**). In this assay presented in FIG. **90**, the compounds were introduced into HeLa cells via lipid mediated transfection.

The importance of phosphorothioate content of the RNA molecule for unassisted delivery was also investigated. FIG. **27** presents the results of a systematic screen that identified that the presence of at least 2-12 phosphorothioates in the guide strand as being highly advantageous for achieving uptake, with 4-8 being the preferred number. FIG. **27** also shows that presence or absence of phosphorothioate modifications in the sense strand did not alter efficacy.

FIGS. **28**-**29** reveal the effects of passive uptake of RNA compounds on gene silencing in primary mouse hepatocytes. nanoRNA molecules were found to be highly effective, especially at a concentration of 1 μM (FIG. **28**). FIGS. **30** and **31** reveal that the RNA compounds associated with the invention were also effective in gene silencing following passive uptake in primary human hepatocytes. The cellular localization of the RNA molecules associated with the invention was examined and compared to the localization of Chol-siRNA (Alnylam) molecules, as shown in FIGS. **32** and **33**.

A summary of 1st generation sd-rxRNA molecules is presented in FIG. **21**. Chemical modifications were introduced into the RNA molecules, at least in part, to increase potency, such as through optimization of nucleotide length and phosphorothioate content, to reduce toxicity, such as through replacing 2'F modifications on the guide strand with other modifications, to improve delivery such as by adding or conjugating the RNA molecules to linker and sterol modalities, and to improve the ease of manufacturing the RNA molecules. FIG. **35** presents schematic depictions of some of the chemical modifications that were screened in 1st generation molecules. Parameters that were optimized for the guide strand included nucleotide length (e.g., 19, 21 and 25 nucleotides), phosphorothioate content (e.g., 0-18 phosphorothioate linkages) and replacement of 2'F groups with 2'OMe and 5 Me C or riboThymidine. Parameters that were optimized for the sense strand included nucleotide length (e.g., 11, 13 and 19 nucleotides), phosphorothioate content (e.g., 0-4 phosphorothioate linkages), and 2'OMe modifications. FIG. **36** summarizes parameters that were screened. For example, the nucleotide length and the phosphorothioate tail length were modified and screened for optimization, as were the additions of 2'OMe C and U modifications. Guide strand length and the length of the phosphorothioate modified stretch of nucleotides were found to influence efficacy (FIGS. **37**-**38**). Phosphorothioate modifications were tolerated in the guide strand and were found to influence passive uptake (FIGS. **39**-**42**).

FIG. **43** presents a schematic revealing guide strand chemical modifications that were screened. FIGS. **44** and **45** reveal that 2' OMe modifications were tolerated in the 3' end of the guide strand. In particular, 2'OMe modifications in positions 1 and 11-18 were well tolerated. The 2'OMe modifications in the seed area were tolerated but resulted in slight reduction of efficacy. Ribo-modifications in the seed were also well tolerated. These data indicate that the molecules associated with the invention offer the significant advantage of having reduced or no 2'F modification content. This is advantageous because 2'F modifications are thought to generate toxicity in vivo. In some instances, a complete substitution of 2'F modifications with 2'OMe was found to lead to some reduction in potency. However, the 2' OMe substituted molecules were still very active. A molecule with 50% reduction in 2'F content (including at positions 11, 16-18 which were changed to 2'OMe modifications), was found to have comparable efficacy to a compound with complete 2'F C and U modification. 2'OMe modification in position was found in some instances to reduce efficacy, although this can be at least partially compensated by 2'OMe modification in position 1 (with chemical phosphate). In some instances, 5 Me C and/or ribothymidine substitution for 2'F modifications led to a reduction in passive uptake efficacy, but increased potency in lipid mediated transfections compared to 2'F modifications. Optimization results for lipid mediated transfection were not necessarily the same as for passive uptake.

Modifications to the sense strand were also developed and tested, as depicted in FIG. **46**. FIG. **47** reveals that in some instances, a sense strand length between 10-15 bases was found to be optimal. For the molecules tested in FIG. **47**, an increase in the sense strand length resulted in reduction of passive uptake, however an increase in sense strand length may be tolerated for some compounds. FIG. **47** also reveals that LNA modification of the sense strand demonstrated similar efficacy to non-LNA containing compounds. In general, the addition of LNA or other thermodynamically stabilizing compounds has been found to be beneficial, in some instances resulting in converting non-functional sequences to functional sequences. FIG. **48** also presents data on sense strand length optimization, while FIG. **49** shows that phosphorothioate modification of the sense strand is not required for passive uptake.

Based on the above-described optimization experiments, 2nd generation RNA molecules were developed. As shown in FIG. **50**, these molecules contained reduced phosphorothioate modification content and reduced 2'F modification content, relative to 1st generation RNA molecules. Significantly, these RNA molecules exhibit spontaneous cellular uptake and efficacy without a delivery vehicle (FIG. **51**). These molecules can achieve self-delivery (i.e., with no transfection reagent) and following self-delivery can exhibit nanomolar activity in cell culture. These molecules can also be delivered using lipid-mediated transfection, and exhibit picomolar activity levels following transfection. Significantly, these molecules exhibit highly efficient uptake, 95% by most cells in cell culture, and are stable for more than three days in the presence of 100% human serum. These molecules are also highly specific and exhibit little or no immune induction. FIGS. **52** and **53** reveal the significance of chemical modifications and the configurations of such modifications in influencing the properties of the RNA molecules associated with the invention.

Linker chemistry was also tested in conjunction with the RNA molecules associated with the invention. As depicted in FIG. **54**, 2^{nd} generation RNA molecules were synthesized with sterol-type molecules attached through TEG and amino caproic acid linkers. Both linkers showed identical potency. This functionality of the RNA molecules, independent of linker chemistry offers additional advantages in terms of scale up and synthesis and demonstrates that the mechanism of function of these RNA molecules is very different from other previously described RNA molecules.

Stability of the chemically modified sd-rxRNA molecules described herein in human serum is shown in FIG. **55** in comparison to unmodified RNA. The duplex molecules were incubated in 75% serum at 37° C. for the indicated periods of time. The level of degradation was determined by running the samples on non-denaturing gels and staining with SYBGR.

FIGS. **56** and **57** present data on cellular uptake of the sd-rxRNA molecules. FIG. **56** shows that minimizing the length of the RNA molecule is importance for cellular uptake, while FIG. **57** presents data showing target gene silencing after spontaneous cellular uptake in mouse PEC-derived macrophages. FIG. **58** demonstrates spontaneous uptake and target gene silencing in primary cells. FIG. **59** shows the results of delivery of sd-rxRNA molecules associated with the invention to RPE cells with no formulation. Imaging with Hoechst and DY547 reveals the clear presence of a signal representing the RNA molecule in the sd-rxRNA sample, while no signal is detectable in the other samples including the samples competing a competing conjugate, an rxRNA, and an untransfected control. FIG. **60** reveals silencing of target gene expression in RPE cells treated with sd-rxRNA molecules associated with the invention following 24-48 hours without any transfection formulation.

FIG. **61** shows further optimization of the chemical/structural composition of sd-rxRNA compounds. In some instances, preferred properties included an antisense strand that was 17-21 nucleotides long, a sense strand that was 10-15 nucleotides long, phosphorothioate modification of 2-12 nucleotides within the single stranded region of the molecule, preferentially phosphorothioate modification of 6-8 nucleotides within the single stranded region, and 2'OMe modification at the majority of positions within the sense strand, with or without phosphorothioate modification. Any linker chemistry can be used to attach the hydrophobic moiety, such as cholesterol, to the 3' end of the sense strand. Version GIib molecules, as shown in FIG. **61**, have no 2'F modifications. Significantly, there is was no impact on efficacy in these molecules.

FIG. **62** demonstrates the superior performance of sd-rxRNA compounds compared to compounds published by Wolfrum et. al. Nature Biotech, 2007. Both generation I and II compounds (GI and GIIa) developed herein show great efficacy in reducing target gene expression. By contrast, when the chemistry described in Wolfrum et al. (all oligos contain cholesterol conjugated to the 3' end of the sense strand) was applied to the same sequence in a context of conventional siRNA (19 bp duplex with two overhang) the compound was practically inactive. These data emphasize the significance of the combination of chemical modifications and assymetrical molecules described herein, producing highly effective RNA compounds.

FIG. **63** shows localization of sd-rxRNA molecules developed herein compared to localization of other RNA molecules such as those described in Soutschek et al. (2004) Nature, 432:173. sd-rxRNA molecules accumulate inside the cells whereas competing conjugate RNAs accumulate on the surface of cells. Significantly, FIG. **64** shows that sd-rxRNA molecules, but not competitor molecules such as those described in Soutschek et al. are internalized within minutes. FIG. **65** compares localization of sd-rxRNA molecules compared to regular siRNA-cholesterol, as described in Soutschek et al. A signal representing the RNA molecule is clearly detected for the sd-rxRNA molecule in tissue culture RPE cells, following local delivery to compromised skin, and following systemic delivery where uptake to the liver is seen. In each case, no signal is detected for the regular siRNA-cholesterol molecule. The sd-rxRNA molecule thus has drastically better cellular and tissue uptake characteristics when compared to conventional cholesterol conjugated siRNAs such as those described in Soutschek et al. The level of uptake is at least order of magnitude higher and is due at least in part to the unique combination of chemistries and conjugated structure. Superior delivery of sd-rxRNA relative to previously described RNA molecules is also demonstrated in FIGS. **66** and **67**.

Based on the analysis of 2^{nd} generation RNA molecules associated with the invention, a screen was performed to identify functional molecules for targeting the SPP1/PPIB gene. As revealed in FIG. **68**, several effective molecules were identified, with 14131 being the most effective. The compounds were added to A-549 cells and then the level of SPP1/PPIB ratio was determined by B-DNA after 48 hours.

FIG. **69** reveals efficient cellular uptake of sd-rxRNA within minutes of exposure. This is a unique characteristics of these molecules, not observed with any other RNAi compounds. Compounds described in Soutschek et al. were used as negative controls. FIG. **70** reveals that the uptake and gene silencing of the sd-rxRNA is effective in multiple different cell types including SH-SY5Y neuroblastoma derived cells, ARPE-19 (retinal pigment epithelium) cells, primary hepatocytes, and primary macrophages. In each case silencing was confirmed by looking at target gene expression by a Branched DNA assay.

FIG. **70** reveals that sd-rxRNA is active in the presence or absence of serum. While a slight reduction in efficacy (2-5 fold) was observed in the presence of serum, this small reduction in efficacy in the presence of serum differentiate the sd-rxRNA molecules from previously described molecules which exhibited a larger reduction in efficacy in the presence of serum. This demonstrated level of efficacy in the presence of serum creates a foundation for in vivo efficacy.

FIG. **72** reveals efficient tissue penetration and cellular uptake upon single intradermal injection. This data indicates the potential of the sd-rxRNA compounds described herein for silencing genes in any dermatology applications, and also represents a model for local delivery of sd-rxRNA compounds. FIG. **73** also demonstrates efficient cellular uptake and in vivo silencing with sd-rxRNA following intradermal injection. Silencing is determined as the level of MAP4K4 knockdown in several individual biopsies taken from the site of injection as compared to biopsies taken from a site injected with a negative control. FIG. **74** reveals that sd-rxRNA compounds has improved blood clearance and induced effective gene silencing in vivo in the liver upon systemic administration. In comparison to the RNA molecules described by Soutschek et al., the level of liver uptake at identical dose level is at least 50 fold higher with the sd-rxRNA molecules. The uptake results in productive silencing. sd-rxRNA compounds are also characterized by improved blood clearance kinetics.

The effect of 5-Methyl C modifications was also examined. FIG. **75** demonstrates that the presence of 5-Methyl C in an

RNAi molecule resulted in increased potency in lipid mediated transfection. This suggests that hydrophobic modification of Cs and Us in an RNAi molecule can be beneficial. These types of modifications can also be used in the context 2' ribose modified bases to ensure optimal stability and efficacy. FIG. **76** presents data showing that incorporation of 5-Methyl C and/or ribothymidine in the guide strand can in some instances reduce efficacy.

FIG. **77** reveals that sd-rxRNA molecules are more effective than competitor molecules such as molecules described in Soutschek et al., in systemic delivery to the liver. A signal representing the RNA molecule is clearly visible in the sample containing sd-rxRNA, while no signal representing the RNA molecule is visible in the sample containing the competitor RNA molecule.

The addition of hydrophobic conjugates to the sd-rxRNA molecules was also explored (FIGS. **78-83**). FIG. **78** presents schematics demonstrating 5-uridyl modifications with improved hydrophobicity characteristics. Incorporation of such modifications into sd-rxRNA compounds can increase cellular and tissue uptake properties. FIG. **78**B presents a new type of RNAi compound modification which can be applied to compounds to improve cellular uptake and pharmacokinetic behavior. Significantly, this type of modification, when applied to sd-rxRNA compounds, may contribute to making such compounds orally available. FIG. **79** presents schematics revealing the structures of synthesized modified sterol-type molecules, where the length and structure of the C17 attached tail is modified. Without wishing to be bound by any theory, the length of the C17 attached tail may contribute to improving in vitro and in vivo efficacy of sd-rxRNA compounds.

FIG. **80** presents a schematic demonstrating the lithocholic acid route to long side chain cholesterols. FIG. **81** presents a schematic demonstrating a route to 5-uridyl phosphoramidite synthesis. FIG. **82** presents a schematic demonstrating synthesis of tri-functional hydroxyprolinol linker for 3'-cholesterol attachment. FIG. **83** presents a schematic demonstrating synthesis of solid support for the manufacture of a shorter asymmetric RNAi compound strand.

A screen was conducted to identify compounds that could effectively silence expression of SPP1 (Osteopontin). Compounds targeting SPP1 were added to A549 cells (using passive transfection), and the level of SPP1 expression was evaluated at 48 hours. Several novel compounds effective in SPP1 silencing were identified. Compounds that were effective in silencing of SPP1 included 14116, 14121, 14131, 14134, 14139, 14149, and 14152 (FIGS. **84-86**). The most potent compound in this assay was 14131 (FIG. **84**). The efficacy of these sd-rxRNA compounds in silencing SPP1 expression was independently validated (FIG. **85**).

A similar screen was conducted to identify compounds that could effectively silence expression of CTGF (FIGS. **86-87**). Compounds that were effective in silencing of CTGF included 14017, 14013, 14016, 14022, 14025, 14027.

Methods

Transfection of sd-rxRNA^{nano}

Lipid Mediated Transfection

sd-rxRNA^{nano} constructs were chemically synthesized (Dharmacon, Lafayette, Colo.) and transfected into HEK293 cells (ATCC, Manassas, Va.) using Lipofectamine RNAiMAX (Invitrogen, Carlsbad, Calif.) according to the manufacturer's instructions. In brief, RNA was diluted to a 12× concentration in Opti-MEM®1 Reduced Serum Media (Invitrogen, Carlsbad, Calif.) and then combined with a 12× concentration of Lipofectamine RNAiMAX. The RNA and transfection reagent were allowed to complex at room temperature for 20 minutes and make a 6× concentration. While complexing, HEK293 cells were washed, trypsinized and counted. The cells were diluted to a concentration recommended by the manufacturer and previously described of 1×10^5 cells/ml. When RNA had completed complexing with the RNAiMAX transfection reagent, 20 ul of the complexes were added to the appropriate well of the 96-well plate in triplicate. Cells were added to each well (100 ul volume) to make the final cell count per well 1×10^4 cells/well. The volume of cells diluted the 6× concentration of complex to 1× (between 10-0.05 nM). Cells were incubated for 24 or 48 hours under normal growth conditions. After 24 or 48 hour incubation, cells were lysed and gene silencing activity was measured using the QuantiGene assay (Panomics, Freemont, Calif.) which employs bDNA hybridization technology. The assay was carried out according to manufacturer's instructions.

Passive Uptake Transfection

sd-rxRNA^{nano} constructs were chemically synthesized (Dharmacon, Lafayette, Colo.). 24 hours prior to transfection, HeLa cells (ATCC, Manassas, Va.) were plated at 1×10^4 cells/well in a 96 well plate under normal growth conditions (DMEM, 10% FBS and 1% Penicillin and Streptomycin). Prior to transfection of HeLa cells, sd-rxRNA^{nano} were diluted to a final concentration of 0.01 uM to 1 uM in Accell siRNA Delivery Media (Dharmacon, Lafayette, Colo.). Normal growth media was aspirated off cells and 100 uL of Accell Delivery media containing the appropriate concentration of sd-rxRNAnano was applied to the cells. 48 hours post transfection, delivery media was aspirated off the cells and normal growth media was applied to cells for an additional 24 hours.

After 48 or 72 hour incubation, cells were lysed and gene silencing activity was measured using the QuantiGene assay (Panomics, Freemont, Calif.) according to manufacturer's instructions.

TABLE 1

ID Number	Oligo Number	Accession number	Gene Name	Gene Symbol
APOB-10167-20-12138	12138	NM_000384	Apolipoprotein B (including Ag(x) antigen)	APOB
APOB-10167-20-*12139*	12139	NM_000384	Apolipoprotein B (including Ag(x) antigen)	APOB
MAP4K4-2931-13-12266	12266	NM_004834	Mitogen-Activated Protein Kinase Kinase Kinase Kinase 4 (MAP4K4), transcript variant 1	MAP4K4
MAP4K4-2931-16-12293	12293	NM_004834	Mitogen-Activated Protein Kinase Kinase Kinase Kinase 4 (MAP4K4), transcript variant 1	MAP4K4

TABLE 1-continued

ID Number	Oligo Number	Accession number	Gene Name	Gene Symbol
MAP4K4-2931-16-12383	12383	NM_004834	Mitogen-Activated Protein Kinase Kinase Kinase Kinase 4 (MAP4K4), transcript variant 1	MAP4K4
MAP4K4-2931-16-12384	12384	NM_004834	Mitogen-Activated Protein Kinase Kinase Kinase Kinase 4 (MAP4K4), transcript variant 1	MAP4K4
MAP4K4-2931-16-12385	12385	NM_004834	Mitogen-Activated Protein Kinase Kinase Kinase Kinase 4 (MAP4K4), transcript variant 1	MAP4K4
MAP4K4-2931-16-12386	12386	NM_004834	Mitogen-Activated Protein Kinase Kinase Kinase Kinase 4 (MAP4K4), transcript variant 1	MAP4K4
MAP4K4-2931-16-12387	12387	NM_004834	Mitogen-Activated Protein Kinase Kinase Kinase Kinase 4 (MAP4K4), transcript variant 1	MAP4K4
MAP4K4-2931-15-12388	12388	NM_004834	Mitogen-Activated Protein Kinase Kinase Kinase Kinase 4 (MAP4K4), transcript variant 1	MAP4K4
MAP4K4-2931-13-12432	12432	NM_004834	Mitogen-Activated Protein Kinase Kinase Kinase Kinase 4 (MAP4K4), transcript variant 1	MAP4K4
MAP4K4-2931-13-12266.2	12266.2	NM_004834	Mitogen-Activated Protein Kinase Kinase Kinase Kinase 4 (MAP4K4), transcript variant 1	MAP4K4
APOB--21-12434	12434	NM_000384	Apolipoprotein B (including Ag(x) antigen)	APOB
APOB--21-12435	12435	NM_000384	Apolipoprotein B (including Ag(x) antigen)	APOB
MAP4K4-2931-16-12451	12451	NM_004834	Mitogen-Activated Protein Kinase Kinase Kinase Kinase 4 (MAP4K4), transcript variant 1	MAP4K4
MAP4K4-2931-16-12452	12452	NM_004834	Mitogen-Activated Protein Kinase Kinase Kinase Kinase 4 (MAP4K4), transcript variant 1	MAP4K4
MAP4K4-2931-16-12453	12453	NM_004834	Mitogen-Activated Protein Kinase Kinase Kinase Kinase 4 (MAP4K4), transcript variant 1	MAP4K4
MAP4K4-2931-17-12454	12454	NM_004834	Mitogen-Activated Protein Kinase Kinase Kinase Kinase 4 (MAP4K4), transcript variant 1	MAP4K4
MAP4K4-2931-17-12455	12455	NM_004834	Mitogen-Activated Protein Kinase Kinase Kinase Kinase 4 (MAP4K4), transcript variant 1	MAP4K4
MAP4K4-2931-19-12456	12456	NM_004834	Mitogen-Activated Protein Kinase Kinase Kinase Kinase 4 (MAP4K4), transcript variant 1	MAP4K4
--27-12480	12480			
--27-12481	12481			
APOB-10167-21-12505	12505	NM_000384	Apolipoprotein B (including Ag(x) antigen)	APOB
APOB-10167-21-12506	12506	NM_000384	Apolipoprotein B (including Ag(x) antigen)	APOB
MAP4K4-2931-16-12539	12539	NM_004834	Mitogen-Activated Protein Kinase Kinase Kinase Kinase 4 (MAP4K4), transcript variant 1	MAP4K4
APOB-10167-21-12505.2	12505.2	NM_000384	Apolipoprotein B (including Ag(x) antigen)	APOB
APOB-10167-21-12506.2	12506.2	NM_000384	Apolipoprotein B (including Ag(x) antigen)	APOB
MAP4K4--13-12565	12565			MAP4K4
MAP4K4-2931-16-12386.2	12386.2	NM_004834	Mitogen-Activated Protein Kinase Kinase Kinase Kinase 4 (MAP4K4), transcript variant 1	MAP4K4
MAP4K4-2931-13-12815	12815	NM_004834	Mitogen-Activated Protein Kinase Kinase Kinase Kinase 4 (MAP4K4), transcript variant 1	MAP4K4
APOB--13-12957	12957	NM_000384	Apolipoprotein B (including Ag(x) antigen)	APOB
MAP4K4--16-12983	12983		Mitogen-Activated Protein Kinase Kinase Kinase Kinase 4 (MAP4K4), transcript variant 1	MAP4K4
MAP4K4--16-12984	12984		Mitogen-Activated Protein Kinase Kinase Kinase Kinase 4 (MAP4K4), transcript variant 1	MAP4K4

TABLE 1-continued

ID Number	Oligo Number	Accession number	Gene Name	Gene Symbol
MAP4K4--16-12985	12985		Mitogen-Activated Protein Kinase Kinase Kinase Kinase 4 (MAP4K4), transcript variant 1	MAP4K4
MAP4K4--16-12986	12986		Mitogen-Activated Protein Kinase Kinase Kinase Kinase 4 (MAP4K4), transcript variant 1	MAP4K4
MAP4K4--16-12987	12987		Mitogen-Activated Protein Kinase Kinase Kinase Kinase 4 (MAP4K4), transcript variant 1	MAP4K4
MAP4K4--16-12988	12988		Mitogen-Activated Protein Kinase Kinase Kinase Kinase 4 (MAP4K4), transcript variant 1	MAP4K4
MAP4K4--16-12989	12989		Mitogen-Activated Protein Kinase Kinase Kinase Kinase 4 (MAP4K4), transcript variant 1	MAP4K4
MAP4K4--16-12990	12990		Mitogen-Activated Protein Kinase Kinase Kinase Kinase 4 (MAP4K4), transcript variant 1	MAP4K4
MAP4K4--16-12991	12991		Mitogen-Activated Protein Kinase Kinase Kinase Kinase 4 (MAP4K4), transcript variant 1	MAP4K4
MAP4K4--16-12992	12992		Mitogen-Activated Protein Kinase Kinase Kinase Kinase 4 (MAP4K4), transcript variant 1	MAP4K4
MAP4K4--16-12993	12993		Mitogen-Activated Protein Kinase Kinase Kinase Kinase 4 (MAP4K4), transcript variant 1	MAP4K4
MAP4K4--16-12994	12994		Mitogen-Activated Protein Kinase Kinase Kinase Kinase 4 (MAP4K4), transcript variant 1	MAP4K4
MAP4K4--16-12995	12995		Mitogen-Activated Protein Kinase Kinase Kinase Kinase 4 (MAP4K4), transcript variant 1	MAP4K4
MAP4K4-2931-19-13012	13012	NM__004834	Mitogen-Activated Protein Kinase Kinase Kinase Kinase 4 (MAP4K4), transcript variant 1	MAP4K4
MAP4K4-2931-19-13016	13016	NM__004834	Mitogen-Activated Protein Kinase Kinase Kinase Kinase 4 (MAP4K4), transcript variant 1	MAP4K4
PPIB--13-13021	13021	NM__000942	Peptidylprolyl Isomerase B (cyclophilin B)	PPIB
pGL3-1172-13-13038	13038	U47296	Cloning vector pGL3-Control	pGL3
pGL3-1172-13-13040	13040	U47296	Cloning vector pGL3-Control	pGL3
--16-13047	13047			
SOD1-530-13-13090	13090	NM__000454	Superoxide Dismutase 1, soluble (amyotrophic lateral sclerosis 1 (adult))	SOD1
SOD1-523-13-13091	13091	NM__000454	Superoxide Dismutase 1, soluble (amyotrophic lateral sclerosis 1 (adult))	SOD1
SOD1-535-13-13092	13092	NM__000454	Superoxide Dismutase 1, soluble (amyotrophic lateral sclerosis 1 (adult))	SOD1
SOD1-536-13-13093	13093	NM__000454	Superoxide Dismutase 1, soluble (amyotrophic lateral sclerosis 1 (adult))	SOD1
SOD1-396-13-13094	13094	NM__000454	Superoxide Dismutase 1, soluble (amyotrophic lateral sclerosis 1 (adult))	SOD1
SOD1-385-13-13095	13095	NM__000454	Superoxide Dismutase 1, soluble (amyotrophic lateral sclerosis 1 (adult))	SOD1
SOD1-195-13-13096	13096	NM__000454	Superoxide Dismutase 1, soluble (amyotrophic lateral sclerosis 1 (adult))	SOD1
APOB-4314-13-13115	13115	NM__000384	Apolipoprotein B (including Ag(x) antigen)	APOB
APOB-3384-13-13116	13116	NM__000384	Apolipoprotein B (including Ag(x) antigen)	APOB
APOB-3547-13-13117	13117	NM__000384	Apolipoprotein B (including Ag(x) antigen)	APOB
APOB-4318-13-13118	13118	NM__000384	Apolipoprotein B (including Ag(x) antigen)	APOB
APOB-3741-13-13119	13119	NM__000384	Apolipoprotein B (including Ag(x) antigen)	APOB

TABLE 1-continued

ID Number	Oligo Number	Accession number	Gene Name	Gene Symbol
PPIB--16-13136	13136	NM_000942	Peptidylprolyl Isomerase B (cyclophilin B)	PPIB
APOB-4314-15-13154	13154	NM_000384	Apolipoprotein B (including Ag(x) antigen)	APOB
APOB-3547-15-13155	13155	NM_000384	Apolipoprotein B (including Ag(x) antigen)	APOB
APOB-4318-15-13157	13157	NM_000384	Apolipoprotein B (including Ag(x) antigen)	APOB
APOB-3741-15-13158	13158	NM_000384	Apolipoprotein B (including Ag(x) antigen)	APOB
APOB--13-13159	13159	NM_000384	Apolipoprotein B (including Ag(x) antigen)	APOB
APOB--15-13160	13160	NM_000384	Apolipoprotein B (including Ag(x) antigen)	APOB
SOD1-530-16-13163	13163	NM_000454	Superoxide Dismutase 1, soluble (amyotrophic lateral sclerosis 1 (adult))	SOD1
SOD1-523-16-13164	13164	NM_000454	Superoxide Dismutase 1, soluble (amyotrophic lateral sclerosis 1 (adult))	SOD1
SOD1-535-16-13165	13165	NM_000454	Superoxide Dismutase 1, soluble (amyotrophic lateral sclerosis 1 (adult))	SOD1
SOD1-536-16-13166	13166	NM_000454	Superoxide Dismutase 1, soluble (amyotrophic lateral sclerosis 1 (adult))	SOD1
SOD1-396-16-13167	13167	NM_000454	Superoxide Dismutase 1, soluble (amyotrophic lateral sclerosis 1 (adult))	SOD1
SOD1-385-16-13168	13168	NM_000454	Superoxide Dismutase 1, soluble (amyotrophic lateral sclerosis 1 (adult))	SOD1
SOD1-195-16-13169	13169	NM_000454	Superoxide Dismutase 1, soluble (amyotrophic lateral sclerosis 1 (adult))	SOD1
pGL3-1172-16-13170	13170	U47296	Cloning vector pGL3-Control	pGL3
pGL3-1172-16-13171	13171	U47296	Cloning vector pGL3-Control	pGL3
MAP4k4-2931-19-13189	13189	NM_004834	Mitogen-Activated Protein Kinase Kinase Kinase Kinase 4 (MAP4K4), transcript variant 1	MAP4k4
CTGF-1222-13-13190	13190	NM_001901.2	connective tissue growth factor	CTGF
CTGF-813-13-13192	13192	NM_001901.2	connective tissue growth factor	CTGF
CTGF-747-13-13194	13194	NM_001901.2	connective tissue growth factor	CTGF
CTGF-817-13-13196	13196	NM_001901.2	connective tissue growth factor	CTGF
CTGF-1174-13-13198	13198	NM_001901.2	connective tissue growth factor	CTGF
CTGF-1005-13-13200	13200	NM_001901.2	connective tissue growth factor	CTGF
CTGF-814-13-13202	13202	NM_001901.2	connective tissue growth factor	CTGF
CTGF-816-13-13204	13204	NM_001901.2	connective tissue growth factor	CTGF
CTGF-1001-13-13206	13206	NM_001901.2	connective tissue growth factor	CTGF
CTGF-1173-13-13208	13208	NM_001901.2	connective tissue growth factor	CTGF
CTGF-749-13-13210	13210	NM_001901.2	connective tissue growth factor	CTGF
CTGF-792-13-13212	13212	NM_001901.2	connective tissue growth factor	CTGF
CTGF-1162-13-13214	13214	NM_001901.2	connective tissue growth factor	CTGF
CTGF-811-13-13216	13216	NM_001901.2	connective tissue growth factor	CTGF
CTGF-797-13-13218	13218	NM_001901.2	connective tissue growth factor	CTGF
CTGF-1175-13-13220	13220	NM_001901.2	connective tissue growth factor	CTGF
CTGF-1172-13-13222	13222	NM_001901.2	connective tissue growth factor	CTGF

TABLE 1-continued

ID Number	Oligo Number	Accession number	Gene Name	Gene Symbol
CTGF-1177-13-13224	13224	NM_001901.2	connective tissue growth factor	CTGF
CTGF-1176-13-13226	13226	NM_001901.2	connective tissue growth factor	CTGF
CTGF-812-13-13228	13228	NM_001901.2	connective tissue growth factor	CTGF
CTGF-745-13-13230	13230	NM_001901.2	connective tissue growth factor	CTGF
CTGF-1230-13-13232	13232	NM_001901.2	connective tissue growth factor	CTGF
CTGF-920-13-13234	13234	NM_001901.2	connective tissue growth factor	CTGF
CTGF-679-13-13236	13236	NM_001901.2	connective tissue growth factor	CTGF
CTGF-992-13-13238	13238	NM_001901.2	connective tissue growth factor	CTGF
CTGF-1045-13-13240	13240	NM_001901.2	connective tissue growth factor	CTGF
CTGF-1231-13-13242	13242	NM_001901.2	connective tissue growth factor	CTGF
CTGF-991-13-13244	13244	NM_001901.2	connective tissue growth factor	CTGF
CTGF-998-13-13246	13246	NM_001901.2	connective tissue growth factor	CTGF
CTGF-1049-13-13248	13248	NM_001901.2	connective tissue growth factor	CTGF
CTGF-1044-13-13250	13250	NM_001901.2	connective tissue growth factor	CTGF
CTGF-1327-13-13252	13252	NM_001901.2	connective tissue growth factor	CTGF
CTGF-1196-13-13254	13254	NM_001901.2	connective tissue growth factor	CTGF
CTGF-562-13-13256	13256	NM_001901.2	connective tissue growth factor	CTGF
CTGF-752-13-13258	13258	NM_001901.2	connective tissue growth factor	CTGF
CTGF-994-13-13260	13260	NM_001901.2	connective tissue growth factor	CTGF
CTGF-1040-13-13262	13262	NM_001901.2	connective tissue growth factor	CTGF
CTGF-1984-13-13264	13264	NM_001901.2	connective tissue growth factor	CTGF
CTGF-2195-13-13266	13266	NM_001901.2	connective tissue growth factor	CTGF
CTGF-2043-13-13268	13268	NM_001901.2	connective tissue growth factor	CTGF
CTGF-1892-13-13270	13270	NM_001901.2	connective tissue growth factor	CTGF
CTGF-1567-13-13272	13272	NM_001901.2	connective tissue growth factor	CTGF
CTGF-1780-13-13274	13274	NM_001901.2	connective tissue growth factor	CTGF
CTGF-2162-13-13276	13276	NM_001901.2	connective tissue growth factor	CTGF
CTGF-1034-13-13278	13278	NM_001901.2	connective tissue growth factor	CTGF
CTGF-2264-13-13280	13280	NM_001901.2	connective tissue growth factor	CTGF
CTGF-1032-13-13282	13282	NM_001901.2	connective tissue growth factor	CTGF
CTGF-1535-13-13284	13284	NM_001901.2	connective tissue growth factor	CTGF
CTGF-1694-13-13286	13286	NM_001901.2	connective tissue growth factor	CTGF
CTGF-1588-13-13288	13288	NM_001901.2	connective tissue growth factor	CTGF
CTGF-928-13-13290	13290	NM_001901.2	connective tissue growth factor	CTGF
CTGF-1133-13-13292	13292	NM_001901.2	connective tissue growth factor	CTGF
CTGF-912-13-13294	13294	NM_001901.2	connective tissue growth factor	CTGF
CTGF-753-13-13296	13296	NM_001901.2	connective tissue growth factor	CTGF
CTGF-918-13-13298	13298	NM_001901.2	connective tissue growth factor	CTGF

TABLE 1-continued

ID Number	Oligo Number	Accession number	Gene Name	Gene Symbol
CTGF-744-13-13300	13300	NM_001901.2	connective tissue growth factor	CTGF
CTGF-466-13-13302	13302	NM_001901.2	connective tissue growth factor	CTGF
CTGF-917-13-13304	13304	NM_001901.2	connective tissue growth factor	CTGF
CTGF-1038-13-13306	13306	NM_001901.2	connective tissue growth factor	CTGF
CTGF-1048-13-13308	13308	NM_001901.2	connective tissue growth factor	CTGF
CTGF-1235-13-13310	13310	NM_001901.2	connective tissue growth factor	CTGF
CTGF-868-13-13312	13312	NM_001901.2	connective tissue growth factor	CTGF
CTGF-1131-13-13314	13314	NM_001901.2	connective tissue growth factor	CTGF
CTGF-1043-13-13316	13316	NM_001901.2	connective tissue growth factor	CTGF
CTGF-751-13-13318	13318	NM_001901.2	connective tissue growth factor	CTGF
CTGF-1227-13-13320	13320	NM_001901.2	connective tissue growth factor	CTGF
CTGF-867-13-13322	13322	NM_001901.2	connective tissue growth factor	CTGF
CTGF-1128-13-13324	13324	NM_001901.2	connective tissue growth factor	CTGF
CTGF-756-13-13326	13326	NM_001901.2	connective tissue growth factor	CTGF
CTGF-1234-13-13328	13328	NM_001901.2	connective tissue growth factor	CTGF
CTGF-916-13-13330	13330	NM_001901.2	connective tissue growth factor	CTGF
CTGF-925-13-13332	13332	NM_001901.2	connective tissue growth factor	CTGF
CTGF-1225-13-13334	13334	NM_001901.2	connective tissue growth factor	CTGF
CTGF-445-13-13336	13336	NM_001901.2	connective tissue growth factor	CTGF
CTGF-446-13-13338	13338	NM_001901.2	connective tissue growth factor	CTGF
CTGF-913-13-13340	13340	NM_001901.2	connective tissue growth factor	CTGF
CTGF-997-13-13342	13342	NM_001901.2	connective tissue growth factor	CTGF
CTGF-277-13-13344	13344	NM_001901.2	connective tissue growth factor	CTGF
CTGF-1052-13-13346	13346	NM_001901.2	connective tissue growth factor	CTGF
CTGF-887-13-13348	13348	NM_001901.2	connective tissue growth factor	CTGF
CTGF-914-13-13350	13350	NM_001901.2	connective tissue growth factor	CTGF
CTGF-1039-13-13352	13352	NM_001901.2	connective tissue growth factor	CTGF
CTGF-754-13-13354	13354	NM_001901.2	connective tissue growth factor	CTGF
CTGF-1130-13-13356	13356	NM_001901.2	connective tissue growth factor	CTGF
CTGF-919-13-13358	13358	NM_001901.2	connective tissue growth factor	CTGF
CTGF-922-13-13360	13360	NM_001901.2	connective tissue growth factor	CTGF
CTGF-746-13-13362	13362	NM_001901.2	connective tissue growth factor	CTGF
CTGF-993-13-13364	13364	NM_001901.2	connective tissue growth factor	CTGF
CTGF-825-13-13366	13366	NM_001901.2	connective tissue growth factor	CTGF
CTGF-926-13-13368	13368	NM_001901.2	connective tissue growth factor	CTGF
CTGF-923-13-13370	13370	NM_001901.2	connective tissue growth factor	CTGF
CTGF-866-13-13372	13372	NM_001901.2	connective tissue growth factor	CTGF
CTGF-563-13-13374	13374	NM_001901.2	connective tissue growth factor	CTGF

TABLE 1-continued

ID Number	Oligo Number	Accession number	Gene Name	Gene Symbol
CTGF-823-13-13376	13376	NM_001901.2	connective tissue growth factor	CTGF
CTGF-1233-13-13378	13378	NM_001901.2	connective tissue growth factor	CTGF
CTGF-924-13-13380	13380	NM_001901.2	connective tissue growth factor	CTGF
CTGF-921-13-13382	13382	NM_001901.2	connective tissue growth factor	CTGF
CTGF-443-13-13384	13384	NM_001901.2	connective tissue growth factor	CTGF
CTGF-1041-13-13386	13386	NM_001901.2	connective tissue growth factor	CTGF
CTGF-1042-13-13388	13388	NM_001901.2	connective tissue growth factor	CTGF
CTGF-755-13-13390	13390	NM_001901.2	connective tissue growth factor	CTGF
CTGF-467-13-13392	13392	NM_001901.2	connective tissue growth factor	CTGF
CTGF-995-13-13394	13394	NM_001901.2	connective tissue growth factor	CTGF
CTGF-927-13-13396	13396	NM_001901.2	connective tissue growth factor	CTGF
SPP1-1025-13-13398	13398	NM_000582.2	Osteopontin	SPP1
SPP1-1049-13-13400	13400	NM_000582.2	Osteopontin	SPP1
SPP1-1051-13-13402	13402	NM_000582.2	Osteopontin	SPP1
SPP1-1048-13-13404	13404	NM_000582.2	Osteopontin	SPP1
SPP1-1050-13-13406	13406	NM_000582.2	Osteopontin	SPP1
SPP1-1047-13-13408	13408	NM_000582.2	Osteopontin	SPP1
SPP1-800-13-13410	13410	NM_000582.2	Osteopontin	SPP1
SPP1-492-13-13412	13412	NM_000582.2	Osteopontin	SPP1
SPP1-612-13-13414	13414	NM_000582.2	Osteopontin	SPP1
SPP1-481-13-13416	13416	NM_000582.2	Osteopontin	SPP1
SPP1-614-13-13418	13418	NM_000582.2	Osteopontin	SPP1
SPP1-951-13-13420	13420	NM_000582.2	Osteopontin	SPP1
SPP1-482-13-13422	13422	NM_000582.2	Osteopontin	SPP1
SPP1-856-13-13424	13424	NM_000582.2	Osteopontin	SPP1
SPP1-857-13-13426	13426	NM_000582.2	Osteopontin	SPP1
SPP1-365-13-13428	13428	NM_000582.2	Osteopontin	SPP1
SPP1-359-13-13430	13430	NM_000582.2	Osteopontin	SPP1
SPP1-357-13-13432	13432	NM_000582.2	Osteopontin	SPP1
SPP1-858-13-13434	13434	NM_000582.2	Osteopontin	SPP1
SPP1-1012-13-13436	13436	NM_000582.2	Osteopontin	SPP1
SPP1-1014-13-13438	13438	NM_000582.2	Osteopontin	SPP1
SPP1-356-13-13440	13440	NM_000582.2	Osteopontin	SPP1
SPP1-368-13-13442	13442	NM_000582.2	Osteopontin	SPP1
SPP1-1011-13-13444	13444	NM_000582.2	Osteopontin	SPP1
SPP1-754-13-13446	13446	NM_000582.2	Osteopontin	SPP1
SPP1-1021-13-13448	13448	NM_000582.2	Osteopontin	SPP1
SPP1-1330-13-13450	13450	NM_000582.2	Osteopontin	SPP1

TABLE 1-continued

ID Number	Oligo Number	Accession number	Gene Name	Gene Symbol
SPP1-346-13-13452	13452	NM_000582.2	Osteopontin	SPP1
SPP1-869-13-13454	13454	NM_000582.2	Osteopontin	SPP1
SPP1-701-13-13456	13456	NM_000582.2	Osteopontin	SPP1
SPP1-896-13-13458	13458	NM_000582.2	Osteopontin	SPP1
SPP1-1035-13-13460	13460	NM_000582.2	Osteopontin	SPP1
SPP1-1170-13-13462	13462	NM_000582.2	Osteopontin	SPP1
SPP1-1282-13-13464	13464	NM_000582.2	Osteopontin	SPP1
SPP1-1537-13-13466	13466	NM_000582.2	Osteopontin	SPP1
SPP1-692-13-13468	13468	NM_000582.2	Osteopontin	SPP1
SPP1-840-13-13470	13470	NM_000582.2	Osteopontin	SPP1
SPP1-1163-13-13472	13472	NM_000582.2	Osteopontin	SPP1
SPP1-789-13-13474	13474	NM_000582.2	Osteopontin	SPP1
SPP1-841-13-13476	13476	NM_000582.2	Osteopontin	SPP1
SPP1-852-13-13478	13478	NM_000582.2	Osteopontin	SPP1
SPP1-209-13-13480	13480	NM_000582.2	Osteopontin	SPP1
SPP1-1276-13-13482	13482	NM_000582.2	Osteopontin	SPP1
SPP1-137-13-13484	13484	NM_000582.2	Osteopontin	SPP1
SPP1-711-13-13486	13486	NM_000582.2	Osteopontin	SPP1
SPP1-582-13-13488	13488	NM_000582.2	Osteopontin	SPP1
SPP1-839-13-13490	13490	NM_000582.2	Osteopontin	SPP1
SPP1-1091-13-13492	13492	NM_000582.2	Osteopontin	SPP1
SPP1-884-13-13494	13494	NM_000582.2	Osteopontin	SPP1
SPP1-903-13-13496	13496	NM_000582.2	Osteopontin	SPP1
SPP1-1090-13-13498	13498	NM_000582.2	Osteopontin	SPP1
SPP1-474-13-13500	13500	NM_000582.2	Osteopontin	SPP1
SPP1-575-13-13502	13502	NM_000582.2	Osteopontin	SPP1
SPP1-671-13-13504	13504	NM_000582.2	Osteopontin	SPP1
SPP1-924-13-13506	13506	NM_000582.2	Osteopontin	SPP1
SPP1-1185-13-13508	13508	NM_000582.2	Osteopontin	SPP1
SPP1-1221-13-13510	13510	NM_000582.2	Osteopontin	SPP1
SPP1-347-13-13512	13512	NM_000582.2	Osteopontin	SPP1
SPP1-634-13-13514	13514	NM_000582.2	Osteopontin	SPP1
SPP1-877-13-13516	13516	NM_000582.2	Osteopontin	SPP1
SPP1-1033-13-13518	13518	NM_000582.2	Osteopontin	SPP1
SPP1-714-13-13520	13520	NM_000582.2	Osteopontin	SPP1
SPP1-791-13-13522	13522	NM_000582.2	Osteopontin	SPP1
SPP1-813-13-13524	13524	NM_000582.2	Osteopontin	SPP1
SPP1-939-13-13526	13526	NM_000582.2	Osteopontin	SPP1

TABLE 1-continued

ID Number	Oligo Number	Accession number	Gene Name	Gene Symbol
SPP1-1161-13-13528	13528	NM_000582.2	Osteopontin	SPP1
SPP1-1164-13-13530	13530	NM_000582.2	Osteopontin	SPP1
SPP1-1190-13-13532	13532	NM_000582.2	Osteopontin	SPP1
SPP1-1333-13-13534	13534	NM_000582.2	Osteopontin	SPP1
SPP1-537-13-13536	13536	NM_000582.2	Osteopontin	SPP1
SPP1-684-13-13538	13538	NM_000582.2	Osteopontin	SPP1
SPP1-707-13-13540	13540	NM_000582.2	Osteopontin	SPP1
SPP1-799-13-13542	13542	NM_000582.2	Osteopontin	SPP1
SPP1-853-13-13544	13544	NM_000582.2	Osteopontin	SPP1
SPP1-888-13-13546	13546	NM_000582.2	Osteopontin	SPP1
SPP1-1194-13-13548	13548	NM_000582.2	Osteopontin	SPP1
SPP1-1279-13-13550	13550	NM_000582.2	Osteopontin	SPP1
SPP1-1300-13-13552	13552	NM_000582.2	Osteopontin	SPP1
SPP1-1510-13-13554	13554	NM_000582.2	Osteopontin	SPP1
SPP1-1543-13-13556	13556	NM_000582.2	Osteopontin	SPP1
SPP1-434-13-13558	13558	NM_000582.2	Osteopontin	SPP1
SPP1-600-13-13560	13560	NM_000582.2	Osteopontin	SPP1
SPP1-863-13-13562	13562	NM_000582.2	Osteopontin	SPP1
SPP1-902-13-13564	13564	NM_000582.2	Osteopontin	SPP1
SPP1-921-13-13566	13566	NM_000582.2	Osteopontin	SPP1
SPP1-154-13-13568	13568	NM_000582.2	Osteopontin	SPP1
SPP1-217-13-13570	13570	NM_000582.2	Osteopontin	SPP1
SPP1-816-13-13572	13572	NM_000582.2	Osteopontin	SPP1
SPP1-882-13-13574	13574	NM_000582.2	Osteopontin	SPP1
SPP1-932-13-13576	13576	NM_000582.2	Osteopontin	SPP1
SPP1-1509-13-13578	13578	NM_000582.2	Osteopontin	SPP1
SPP1-157-13-13580	13580	NM_000582.2	Osteopontin	SPP1
SPP1-350-13-13582	13582	NM_000582.2	Osteopontin	SPP1
SPP1-511-13-13584	13584	NM_000582.2	Osteopontin	SPP1
SPP1-605-13-13586	13586	NM_000582.2	Osteopontin	SPP1
SPP1-811-13-13588	13588	NM_000582.2	Osteopontin	SPP1
SPP1-892-13-13590	13590	NM_000582.2	Osteopontin	SPP1
SPP1-922-13-13592	13592	NM_000582.2	Osteopontin	SPP1
SPP1-1169-13-13594	13594	NM_000582.2	Osteopontin	SPP1
SPP1-1182-13-13596	13596	NM_000582.2	Osteopontin	SPP1
SPP1-1539-13-13598	13598	NM_000582.2	Osteopontin	SPP1
SPP1-1541-13-13600	13600	NM_000582.2	Osteopontin	SPP1
SPP1-427-13-13602	13602	NM_000582.2	Osteopontin	SPP1

TABLE 1-continued

ID Number	Oligo Number	Accession number	Gene Name	Gene Symbol
SPP1-533-13-13604	13604	NM_000582.2	Osteopontin	SPP1
APOB--13-13763	13763	NM_000384	Apolipoprotein B (including Ag(x) antigen)	APOB
APOB--13-13764	13764	NM_000384	Apolipoprotein B (including Ag(x) antigen)	APOB
MAP4K4--16-13766	13766			MAP4K4
PPIB--13-13767	13767	NM_000942	peptidylprolyl isomerase B (cyclophilin B)	PPIB
PPIB--15-13768	13768	NM_000942	peptidylprolyl isomerase B (cyclophilin B)	PPIB
PPIB--17-13769	13769	NM_000942	peptidylprolyl isomerase B (cyclophilin B)	PPIB
MAP4K4--16-13939	13939			MAP4K4
APOB-4314-16-13940	13940	NM_000384	Apolipoprotein B (including Ag(x) antigen)	APOB
APOB-4314-17-13941	13941	NM_000384	Apolipoprotein B (including Ag(x) antigen)	APOB
APOB--16-13942	13942	NM_000384	Apolipoprotein B (including Ag(x) antigen)	APOB
APOB--18-13943	13943	NM_000384	Apolipoprotein B (including Ag(x) antigen)	APOB
APOB--17-13944	13944	NM_000384	Apolipoprotein B (including Ag(x) antigen)	APOB
APOB--19-13945	13945	NM_000384	Apolipoprotein B (including Ag(x) antigen)	APOB
APOB-4314-16-13946	13946	NM_000384	Apolipoprotein B (including Ag(x) antigen)	APOB
APOB-4314-17-13947	13947	NM_000384	Apolipoprotein B (including Ag(x) antigen)	APOB
APOB--16-13948	13948	NM_000384	Apolipoprotein B (including Ag(x) antigen)	APOB
APOB--17-13949	13949	NM_000384	Apolipoprotein B (including Ag(x) antigen)	APOB
APOB--16-13950	13950	NM_000384	Apolipoprotein B (including Ag(x) antigen)	APOB
APOB--18-13951	13951	NM_000384	Apolipoprotein B (including Ag(x) antigen)	APOB
APOB--17-13952	13952	NM_000384	Apolipoprotein B (including Ag(x) antigen)	APOB
APOB--19-13953	13953	NM_000384	Apolipoprotein B (including Ag(x) antigen)	APOB
MAP4K4--16-13766.2	13766.2			MAP4K4
CTGF-1222-16-13980	13980	NM_001901.2	connective tissue growth factor	CTGF
CTGF-813-16-13981	13981	NM_001901.2	connective tissue growth factor	CTGF
CTGF-747-16-13982	13982	NM_001901.2	connective tissue growth factor	CTGF
CTGF-817-16-13983	13983	NM_001901.2	connective tissue growth factor	CTGF
CTGF-1174-16-13984	13984	NM_001901.2	connective tissue growth factor	CTGF
CTGF-1005-16-13985	13985	NM_001901.2	connective tissue growth factor	CTGF
CTGF-814-16-13986	13986	NM_001901.2	connective tissue growth factor	CTGF
CTGF-816-16-13987	13987	NM_001901.2	connective tissue growth factor	CTGF
CTGF-1001-16-13988	13988	NM_001901.2	connective tissue growth factor	CTGF
CTGF-1173-16-13989	13989	NM_001901.2	connective tissue growth factor	CTGF
CTGF-749-16-13990	13990	NM_001901.2	connective tissue growth factor	CTGF
CTGF-792-16-13991	13991	NM_001901.2	connective tissue growth factor	CTGF
CTGF-1162-16-13992	13992	NM_001901.2	connective tissue growth factor	CTGF
CTGF-811-16-13993	13993	NM_001901.2	connective tissue growth factor	CTGF
CTGF-797-16-13994	13994	NM_001901.2	connective tissue growth factor	CTGF

TABLE 1-continued

ID Number	Oligo Number	Accession number	Gene Name	Gene Symbol
CTGF-1175-16-13995	13995	NM_001901.2	connective tissue growth factor	CTGF
CTGF-1172-16-13996	13996	NM_001901.2	connective tissue growth factor	CTGF
CTGF-1177-16-13997	13997	NM_001901.2	connective tissue growth factor	CTGF
CTGF-1176-16-13998	13998	NM_001901.2	connective tissue growth factor	CTGF
CTGF-812-16-13999	13999	NM_001901.2	connective tissue growth factor	CTGF
CTGF-745-16-14000	14000	NM_001901.2	connective tissue growth factor	CTGF
CTGF-1230-16-14001	14001	NM_001901.2	connective tissue growth factor	CTGF
CTGF-920-16-14002	14002	NM_001901.2	connective tissue growth factor	CTGF
CTGF-679-16-14003	14003	NM_001901.2	connective tissue growth factor	CTGF
CTGF-992-16-14004	14004	NM_001901.2	connective tissue growth factor	CTGF
CTGF-1045-16-14005	14005	NM_001901.2	connective tissue growth factor	CTGF
CTGF-1231-16-14006	14006	NM_001901.2	connective tissue growth factor	CTGF
CTGF-991-16-14007	14007	NM_001901.2	connective tissue growth factor	CTGF
CTGF-998-16-14008	14008	NM_001901.2	connective tissue growth factor	CTGF
CTGF-1049-16-14009	14009	NM_001901.2	connective tissue growth factor	CTGF
CTGF-1044-16-14010	14010	NM_001901.2	connective tissue growth factor	CTGF
CTGF-1327-16-14011	14011	NM_001901.2	connective tissue growth factor	CTGF
CTGF-1196-16-14012	14012	NM_001901.2	connective tissue growth factor	CTGF
CTGF-562-16-14013	14013	NM_001901.2	connective tissue growth factor	CTGF
CTGF-752-16-14014	14014	NM_001901.2	connective tissue growth factor	CTGF
CTGF-994-16-14015	14015	NM_001901.2	connective tissue growth factor	CTGF
CTGF-1040-16-14016	14016	NM_001901.2	connective tissue growth factor	CTGF
CTGF-1984-16-14017	14017	NM_001901.2	connective tissue growth factor	CTGF
CTGF-2195-16-14018	14018	NM_001901.2	connective tissue growth factor	CTGF
CTGF-2043-16-14019	14019	NM_001901.2	connective tissue growth factor	CTGF
CTGF-1892-16-14020	14020	NM_001901.2	connective tissue growth factor	CTGF
CTGF-1567-16-14021	14021	NM_001901.2	connective tissue growth factor	CTGF
CTGF-1780-16-14022	14022	NM_001901.2	connective tissue growth factor	CTGF
CTGF-2162-16-14023	14023	NM_001901.2	connective tissue growth factor	CTGF
CTGF-1034-16-14024	14024	NM_001901.2	connective tissue growth factor	CTGF
CTGF-2264-16-14025	14025	NM_001901.2	connective tissue growth factor	CTGF
CTGF-1032-16-14026	14026	NM_001901.2	connective tissue growth factor	CTGF
CTGF-1535-16-14027	14027	NM_001901.2	connective tissue growth factor	CTGF
CTGF-1694-16-14028	14028	NM_001901.2	connective tissue growth factor	CTGF
CTGF-1588-16-14029	14029	NM_001901.2	connective tissue growth factor	CTGF
CTGF-928-16-14030	14030	NM_001901.2	connective tissue growth factor	CTGF
CTGF-1133-16-14031	14031	NM_001901.2	connective tissue growth factor	CTGF
CTGF-912-16-14032	14032	NM_001901.2	connective tissue growth factor	CTGF

TABLE 1-continued

ID Number	Oligo Number	Accession number	Gene Name	Gene Symbol
CTGF-753-16-14033	14033	NM__001901.2	connective tissue growth factor	CTGF
CTGF-918-16-14034	14034	NM__001901.2	connective tissue growth factor	CTGF
CTGF-744-16-14035	14035	NM__001901.2	connective tissue growth factor	CTGF
CTGF-466-16-14036	14036	NM__001901.2	connective tissue growth factor	CTGF
CTGF-917-16-14037	14037	NM__001901.2	connective tissue growth factor	CTGF
CTGF-1038-16-14038	14038	NM__001901.2	connective tissue growth factor	CTGF
CTGF-1048-16-14039	14039	NM__001901.2	connective tissue growth factor	CTGF
CTGF-1235-16-14040	14040	NM__001901.2	connective tissue growth factor	CTGF
CTGF-868-16-14041	14041	NM__001901.2	connective tissue growth factor	CTGF
CTGF-1131-16-14042	14042	NM__001901.2	connective tissue growth factor	CTGF
CTGF-1043-16-14043	14043	NM__001901.2	connective tissue growth factor	CTGF
CTGF-751-16-14044	14044	NM__001901.2	connective tissue growth factor	CTGF
CTGF-1227-16-14045	14045	NM__001901.2	connective tissue growth factor	CTGF
CTGF-867-16-14046	14046	NM__001901.2	connective tissue growth factor	CTGF
CTGF-1128-16-14047	14047	NM__001901.2	connective tissue growth factor	CTGF
CTGF-756-16-14048	14048	NM__001901.2	connective tissue growth factor	CTGF
CTGF-1234-16-14049	14049	NM__001901.2	connective tissue growth factor	CTGF
CTGF-916-16-14050	14050	NM__001901.2	connective tissue growth factor	CTGF
CTGF-925-16-14051	14051	NM__001901.2	connective tissue growth factor	CTGF
CTGF-1225-16-14052	14052	NM__001901.2	connective tissue growth factor	CTGF
CTGF-445-16-14053	14053	NM__001901.2	connective tissue growth factor	CTGF
CTGF-446-16-14054	14054	NM__001901.2	connective tissue growth factor	CTGF
CTGF-913-16-14055	14055	NM__001901.2	connective tissue growth factor	CTGF
CTGF-997-16-14056	14056	NM__001901.2	connective tissue growth factor	CTGF
CTGF-277-16-14057	14057	NM__001901.2	connective tissue growth factor	CTGF
CTGF-1052-16-14058	14058	NM__001901.2	connective tissue growth factor	CTGF
CTGF-887-16-14059	14059	NM__001901.2	connective tissue growth factor	CTGF
CTGF-914-16-14060	14060	NM__001901.2	connective tissue growth factor	CTGF
CTGF-1039-16-14061	14061	NM__001901.2	connective tissue growth factor	CTGF
CTGF-754-16-14062	14062	NM__001901.2	connective tissue growth factor	CTGF
CTGF-1130-16-14063	14063	NM__001901.2	connective tissue growth factor	CTGF
CTGF-919-16-14064	14064	NM__001901.2	connective tissue growth factor	CTGF
CTGF-922-16-14065	14065	NM__001901.2	connective tissue growth factor	CTGF
CTGF-746-16-14066	14066	NM__001901.2	connective tissue growth factor	CTGF
CTGF-993-16-14067	14067	NM__001901.2	connective tissue growth factor	CTGF
CTGF-825-16-14068	14068	NM__001901.2	connective tissue growth factor	CTGF
CTGF-926-16-14069	14069	NM__001901.2	connective tissue growth factor	CTGF
CTGF-923-16-14070	14070	NM__001901.2	connective tissue growth factor	CTGF

TABLE 1-continued

ID Number	Oligo Number	Accession number	Gene Name	Gene Symbol
CTGF-866-16-14071	14071	NM_001901.2	connective tissue growth factor	CTGF
CTGF-563-16-14072	14072	NM_001901.2	connective tissue growth factor	CTGF
CTGF-823-16-14073	14073	NM_001901.2	connective tissue growth factor	CTGF
CTGF-1233-16-14074	14074	NM_001901.2	connective tissue growth factor	CTGF
CTGF-924-16-14075	14075	NM_001901.2	connective tissue growth factor	CTGF
CTGF-921-16-14076	14076	NM_001901.2	connective tissue growth factor	CTGF
CTGF-443-16-14077	14077	NM_001901.2	connective tissue growth factor	CTGF
CTGF-1041-16-14078	14078	NM_001901.2	connective tissue growth factor	CTGF
CTGF-1042-16-14079	14079	NM_001901.2	connective tissue growth factor	CTGF
CTGF-755-16-14080	14080	NM_001901.2	connective tissue growth factor	CTGF
CTGF-467-16-14081	14081	NM_001901.2	connective tissue growth factor	CTGF
CTGF-995-16-14082	14082	NM_001901.2	connective tissue growth factor	CTGF
CTGF-927-16-14083	14083	NM_001901.2	connective tissue growth factor	CTGF
SPP1-1091-16-14131	14131	NM_000582.2	Osteopontin	SPP1
PPIB--16-14188	14188	NM_000942	peptidylprolyl isomerase B (cyclophilin B)	PPIB
PPIB--17-14189	14189	NM_000942	peptidylprolyl isomerase B (cyclophilin B)	PPIB
PPIB--18-14190	14190	NM_000942	peptidylprolyl isomerase B (cyclophilin B)	PPIB
pGL3-1172-16-14386	14386	U47296	Cloning vector pGL3-Control	pGL3
pGL3-1172-16-14387	14387	U47296	Cloning vector pGL3-Control	pGL3
MAP4K4-2931-25-14390	14390	NM_004834	Mitogen-Activated Protein Kinase Kinase Kinase Kinase 4 (MAP4K4), transcript variant 1	MAP4K4
miR-122--23-14391	14391			miR-122
	14084	NM_000582.2	Osteopontin	SPP1
	14085	NM_000582.2	Osteopontin	SPP1
	14086	NM_000582.2	Osteopontin	SPP1
	14087	NM_000582.2	Osteopontin	SPP1
	14088	NM_000582.2	Osteopontin	SPP1
	14089	NM_000582.2	Osteopontin	SPP1
	14090	NM_000582.2	Osteopontin	SPP1
	14091	NM_000582.2	Osteopontin	SPP1
	14092	NM_000582.2	Osteopontin	SPP1
	14093	NM_000582.2	Osteopontin	SPP1
	14094	NM_000582.2	Osteopontin	SPP1
	14095	NM_000582.2	Osteopontin	SPP1
	14096	NM_000582.2	Osteopontin	SPP1
	14097	NM_000582.2	Osteopontin	SPP1
	14098	NM_000582.2	Osteopontin	SPP1
	14099	NM_000582.2	Osteopontin	SPP1
	14100	NM_000582.2	Osteopontin	SPP1
	14101	NM_000582.2	Osteopontin	SPP1
	14102	NM_000582.2	Osteopontin	SPP1
	14103	NM_000582.2	Osteopontin	SPP1
	14104	NM_000582.2	Osteopontin	SPP1
	14105	NM_000582.2	Osteopontin	SPP1
	14106	NM_000582.2	Osteopontin	SPP1
	14107	NM_000582.2	Osteopontin	SPP1
	14108	NM_000582.2	Osteopontin	SPP1
	14109	NM_000582.2	Osteopontin	SPP1
	14110	NM_000582.2	Osteopontin	SPP1
	14111	NM_000582.2	Osteopontin	SPP1
	14112	NM_000582.2	Osteopontin	SPP1
	14113	NM_000582.2	Osteopontin	SPP1
	14114	NM_000582.2	Osteopontin	SPP1
	14115	NM_000582.2	Osteopontin	SPP1
	14116	NM_000582.2	Osteopontin	SPP1
	14117	NM_000582.2	Osteopontin	SPP1

TABLE 1-continued

ID Number	Oligo Number	Accession number	Gene Name	Gene Symbol
	14118	NM_000582.2	Osteopontin	SPP1
	14119	NM_000582.2	Osteopontin	SPP1
	14120	NM_000582.2	Osteopontin	SPP1
	14121	NM_000582.2	Osteopontin	SPP1
	14122	NM_000582.2	Osteopontin	SPP1
	14123	NM_000582.2	Osteopontin	SPP1
	14124	NM_000582.2	Osteopontin	SPP1
	14125	NM_000582.2	Osteopontin	SPP1
	14126	NM_000582.2	Osteopontin	SPP1
	14127	NM_000582.2	Osteopontin	SPP1
	14128	NM_000582.2	Osteopontin	SPP1
	14129	NM_000582.2	Osteopontin	SPP1
	14130	NM_000582.2	Osteopontin	SPP1
	14132	NM_000582.2	Osteopontin	SPP1
	14133	NM_000582.2	Osteopontin	SPP1
	14134	NM_000582.2	Osteopontin	SPP1
	14135	NM_000582.2	Osteopontin	SPP1
	14136	NM_000582.2	Osteopontin	SPP1
	14137	NM_000582.2	Osteopontin	SPP1
	14138	NM_000582.2	Osteopontin	SPP1
	14139	NM_000582.2	Osteopontin	SPP1
	14140	NM_000582.2	Osteopontin	SPP1
	14141	NM_000582.2	Osteopontin	SPP1
	14142	NM_000582.2	Osteopontin	SPP1
	14143	NM_000582.2	Osteopontin	SPP1
	14144	NM_000582.2	Osteopontin	SPP1
	14145	NM_000582.2	Osteopontin	SPP1
	14146	NM_000582.2	Osteopontin	SPP1
	14147	NM_000582.2	Osteopontin	SPP1
	14148	NM_000582.2	Osteopontin	SPP1
	14149	NM_000582.2	Osteopontin	SPP1
	14150	NM_000582.2	Osteopontin	SPP1
	14151	NM_000582.2	Osteopontin	SPP1
	14152	NM_000582.2	Osteopontin	SPP1
	14153	NM_000582.2	Osteopontin	SPP1
	14154	NM_000582.2	Osteopontin	SPP1
	14155	NM_000582.2	Osteopontin	SPP1
	14156	NM_000582.2	Osteopontin	SPP1
	14157	NM_000582.2	Osteopontin	SPP1
	14158	NM_000582.2	Osteopontin	SPP1
	14159	NM_000582.2	Osteopontin	SPP1
	14160	NM_000582.2	Osteopontin	SPP1
	14161	NM_000582.2	Osteopontin	SPP1
	14162	NM_000582.2	Osteopontin	SPP1
	14163	NM_000582.2	Osteopontin	SPP1
	14164	NM_000582.2	Osteopontin	SPP1
	14165	NM_000582.2	Osteopontin	SPP1
	14166	NM_000582.2	Osteopontin	SPP1
	14167	NM_000582.2	Osteopontin	SPP1
	14168	NM_000582.2	Osteopontin	SPP1
	14169	NM_000582.2	Osteopontin	SPP1
	14170	NM_000582.2	Osteopontin	SPP1
	14171	NM_000582.2	Osteopontin	SPP1
	14172	NM_000582.2	Osteopontin	SPP1
	14173	NM_000582.2	Osteopontin	SPP1
	14174	NM_000582.2	Osteopontin	SPP1
	14175	NM_000582.2	Osteopontin	SPP1
	14176	NM_000582.2	Osteopontin	SPP1
	14177	NM_000582.2	Osteopontin	SPP1
	14178	NM_000582.2	Osteopontin	SPP1
	14179	NM_000582.2	Osteopontin	SPP1
	14180	NM_000582.2	Osteopontin	SPP1
	14181	NM_000582.2	Osteopontin	SPP1
	14182	NM_000582.2	Osteopontin	SPP1
	14183	NM_000582.2	Osteopontin	SPP1
	14184	NM_000582.2	Osteopontin	SPP1
	14185	NM_000582.2	Osteopontin	SPP1
	14186	NM_000582.2	Osteopontin	SPP1
	14187	NM_000582.2	Osteopontin	SPP1

TABLE 2

Antisense backbone, chemistry, and sequence information. o: phosphodiester; s: phosphorothioate; P: 5'phosphorylation; 0: 2'-OH; F: 2'-fluoro; m: 2'O-methyl; +: LNA modification. Capital letters in the sequence signify riobonucleotides, lower case letters signify deoxyribonucleotides.

ID Number	Oligo Number	AntiSense Backbone	AntiSense Chemistry	AntiSense Sequence	SEQ ID NO:
APOB-10167-20-12138	12138	oooooooooooooooooo	00000000000000000000m	AUUGGUAUUCAGUGUGAUG	1
APOB-10167-20-12139	12139	oooooooooooooooooo	00000000000000000000m	AUUCGUAUUGAGUCUGAUC	2
MAP4K4-2931-13-12266	12266				
MAP4K4-2931-16-12293	12293	oooooooooooooooooo	Pf000fffff0f0000fff0	UAGACUUCCACAGAACUCU	3
MAP4K4-2931-16-12383	12383	oooooooooooooooooo	0000000000000000000	UAGACUUCCACAGAACUCU	4
MAP4K4-2931-16-12384	12384	oooooooooooooooooo	P0000000000000000000	UAGACUUCCACAGAACUCU	5
MAP4K4-2931-16-12385	12385	oooooooooooooooooo	Pf000fffff0f0000fff0	UAGACUUCCACAGAACUCU	6
MAP4K4-2931-16-12386	12386	ooooooooooosssssssso	Pf000fffff0f0000fff0	UAGACUUCCACAGAACUCU	7
MAP4K4-2931-16-12387	12387	ooooooooooosssssssso	P0000000000000000000	UAGACUUCCACAGAACUCU	8
MAP4K4-2931-15-12388	12388	oooooooooooooooo	00000000000000000	UAGACUUCCACAGAACU	9
MAP4K4-2931-13-12432	12432				
MAP4K4-2931-13-12266.2	12266.2				
APOB--21-12434	12434	oooooooooooooooooooo	00000000000000000000m	AUUGGUAUUCAGUGUGAUGAC	10
APOB--21-12435	12435	oooooooooooooooooooo	00000000000000000000m	AUUCGUAUUGAGUCUGAUCAC	11
MAP4K4-2931-16-12451	12451	ooooooooooosssssssso	Pf000fffff0f0000ffmm	UAGACUUCCACAGAACUCU	12
MAP4K4-2931-16-12452	12452	ooooooooooosssssssso	Pm000fffff0f0000ffmm	UAGACUUCCACAGAACUCU	13
MAP4K4-2931-16-12453	12453	oooooossssssssssso	Pm000fffff0f0000ffmm	UAGACUUCCACAGAACUCU	14
MAP4K4-2931-17-12454	12454	ooooooooooooosssssssso	Pm000fffff0f0000ffffmm	UAGACUUCCACAGAACUCUUC	15

TABLE 2-continued

Antisense backbone, chemistry, and sequence information. o: phosphodiester; s: phosphorothioate; P: 5'phosphorylation; 0: 2'-OH; F: 2'-fluoro; m: 2'O-methyl; +: LNA modification. Capital letters in the sequence signify riobonucleotides, lower case letters signify deoxyribonucleotides.

ID Number	Oligo Number	AntiSense Backbone	AntiSense Chemistry	AntiSense Sequence	SEQ ID NO:
MAP4K4-2931-17-12455	12455	oooooooooosssss sssssso	Pm000fffff0f00 00ffffmm	UAGACUUCCACAGAACU CUUC	16
MAP4K4-2931-19-12456	12456	oooooooooooos ssssssssssso	Pm000fffff0f00 00ffffff00mm	UAGACUUCCACAGAACU CUUCAAAG	17
--27-12480	12480				
--27-12481	12481				
APOB-10167-21-12505	12505	ooooooooooooo oooooooos	00000000000000 000000m	AUUGGUAUUCAGUGUGA UGAC	18
APOB-10167-21-12506	12506	ooooooooooooo oooooooos	00000000000000 000000m	AUUCGUAUUGAGUCUGA UCAC	19
MAP4K4-2931-16-12539	12539	oooooooooooss ssssss	Pf000fffff0f00 00fff0	UAGACUUCCACAGAACU CU	20
APOB-10167-21-12505.2	12505.2	ooooooooooooo oooooooo	00000000000000 000000m	AUUGGUAUUCAGUGUGA UGAC	21
APOB-10167-21-12506.2	12506.2	ooooooooooooo oooooooo	00000000000000 000000m	AUUCGUAUUGAGUCUGA UCAC	22
MAP4K4--13-12565	12565				
MAP4K4-2931-16-12386.2	12386.2	oooooooooosss ssssso	Pf000fffff0f00 00fff0	UAGACUUCCACAGAACU CU	23
MAP4K4-2931-13-12815	12815				
APOB--13-12957	12957				
MAP4K4--16-12983	12983	oooooooooooos ssssso	Pm000fffff0m00 00mmm0	uagacuuccacagaacu cu	24
MAP4K4--16-12984	12984	oooooooooooos sssss	Pm000fffff0m00 00mmm0	uagacuuccacagaacu cu	25
MAP4K4--16-12985	12985	oooooooooooos ssssso	Pm000fffff0m00 00mmm0	uagacuuccacagaacu cu	26
MAP4K4--16-12986	12986	oooooooooosss ssssso	Pf000fffff0f00 00fff0	UAGACUUCCACAGAACU CU	27
MAP4K4--16-12987	12987	ooooooooooooo ssssss	P0000f00ff0m00 00m0m0	UagacUUccacagaacU cU	28
MAP4K4--16-12988	12988	ooooooooooooo ssssss	P0000f00ff0m00 00m0m0	UagacUUccacagaacU cu	29
MAP4K4--16-12989	12989	ooooooooooooo ssssss	P0000ff0ff0m00 00m0m0	UagacuUccacagaacU cu	30
MAP4K4--16-12990	12990	ooooooooooooo ssssss	Pf0000ff000000 000m00	uagaCuuCCaCagaaCu Cu	31

TABLE 2-continued

Antisense backbone, chemistry, and sequence information. o: phosphodiester; s: phosphorothioate; P: 5'phosphorylation; 0: 2'-OH; F: 2'-fluoro; m: 2'O-methyl; +: LNA modification. Capital letters in the sequence signify riobonucleotides, lower case letters signify deoxyribonucleotides.

ID Number	Oligo Number	AntiSense Backbone	AntiSense Chemistry	AntiSense Sequence	SEQ ID NO:
MAP4K4--16-12991	12991	ooooooooooooosssss s	Pf0000fff00m00000mm0	uagaCuucCacagaaCucu	32
MAP4K4--16-12992	12992	ooooooooooooossssss	Pf000fffff0000000m00	uagacuuccaCagaaCuCu	33
MAP4K4--16-12993	12993	ooooooooooooossssss	P0000000000000000000	UagaCUUCCaCagaaCUCU	34
MAP4K4--16-12994	12994	ooooooooooooossssss	P0000f0f0f0000000m00	UagacUuCcaCagaaCuCu	35
MAP4K4--16-12995	12995	ooooooooooooossssso	Pf000fffff0000000000	uagacuuccaCagaaCUCU	36
MAP4K4-2931-19-13012	13012				
MAP4K4-2931-19-13016	13016				
PPIB--13-13021	13021				
pGL3-1172-13-13038	13038				
pGL3-1172-13-13040	13040				
--16-13047	13047	ooooooooooooosssss	Pm000000000m0000mmm0	UAGACUUCCACAGAACUCU	37
SOD1-530-13-13090	13090				
SOD1-523-13-13091	13091				
SOD1-535-13-13092	13092				
SOD1-536-13-13093	13093				
SOD1-396-13-13094	13094				
SOD1-385-13-13095	13095				
SOD1-195-13-13096	13096				
APOB-4314-13-13115	13115				
APOB-3384-13-13116	13116				
APOB-3547-13-13117	13117				
APOB-4318-13-13118	13118				
APOB-3741-13-13119	13119				

TABLE 2-continued

Antisense backbone, chemistry, and sequence information. o: phosphodiester; s: phosphorothioate; P: 5'phosphorylation; 0: 2'-OH; F: 2'-fluoro; m: 2'O-methyl; +: LNA modification. Capital letters in the sequence signify riobonucleotides, lower case letters signify deoxyribonucleotides.

ID Number	Oligo Number	AntiSense Backbone	AntiSense Chemistry	AntiSense Sequence	SEQ ID NO:
PPIB--16-13136	13136	ooooooooooooosssss	Pm0fffff0f00mm000mm0	UGUUUUUGUAGCCAAAUCC	38
APOB-4314-15-13154	13154				
APOB-3547-15-13155	13155				
APOB-4318-15-13157	13157				
APOB-3741-15-13158	13158				
APOB--13-13159	13159				
APOB--15-13160	13160				
SOD1-530-16-13163	13163	oooooooooooosssssso	Pm0fffffff0mmmmm0m0	UACUUUCUUCAUUUCCACC	39
SOD1-523-16-13164	13164	oooooooooooosssssso	Pmff0fffff0fmmmm0mm0	UUCAUUUCCACCUUUGCCC	40
SOD1-535-16-13165	13165	oooooooooooosssssso	Pmfff0f0ffffmmmm0mm0	CUUUGUACUUUCUUCAUUU	41
SOD1-536-16-13166	13166	oooooooooooosssssso	Pmffff0f0fffmmmmm0m0	UCUUUGUACUUUCUUCAUU	42
SOD1-396-16-13167	13167	oooooooooooosssssso	Pmf00f00ff0f0mm0mmm0	UCAGCAGUCACAUUGCCCA	43
SOD1-385-16-13168	13168	oooooooooooosssssso	Pmff0fff000fmmmm00m0	AUUGCCCAAGUCUCCAACA	44
SOD1-195-16-13169	13169	oooooooooooosssssso	Pmfff0fff0000mm00m00	UUCUGCUCGAAAUUGAUGA	45
pGL3-1172-16-13170	13170	oooooooooooosssssso	Pm00ff0f0ffm0ff00mm0	AAAUCGUAUUUGUCAAUCA	46
pGL3-1172-16-13171	13171	ooooooooooooosssssss	Pm00ff0f0ffm0ff00mm0	AAAUCGUAUUUGUCAAUCA	47
MAP4k4-2931-19-13189	13189	oooooooooooooooooo	0000000000000000000	UAGACUUCCACAGAACUCU	48
CTGF-1222-13-13190	13190				
CTGF-813-13-13192	13192				
CTGF-747-13-13194	13194				
CTGF-817-13-13196	13196				
CTGF-1174-13-13198	13198				
CTGF-1005-13-13200	13200				

TABLE 2-continued

Antisense backbone, chemistry, and sequence information. o: phosphodiester; s: phosphorothioate; P: 5'phosphorylation; 0: 2'-OH; F: 2'-fluoro; m: 2'O-methyl; +: LNA modification. Capital letters in the sequence signify riobonucleotides, lower case letters signify deoxyribonucleotides.

ID Number	Oligo Number	AntiSense Backbone	AntiSense Chemistry	AntiSense Sequence	SEQ ID NO:
CTGF-814-13-13202	13202				
CTGF-816-13-13204	13204				
CTGF-1001-13-13206	13206				
CTGF-1173-13-13208	13208				
CTGF-749-13-13210	13210				
CTGF-792-13-13212	13212				
CTGF-1162-13-13214	13214				
CTGF-811-13-13216	13216				
CTGF-797-13-13218	13218				
CTGF-1175-13-13220	13220				
CTGF-1172-13-13222	13222				
CTGF-1177-13-13224	13224				
CTGF-1176-13-13226	13226				
CTGF-812-13-13228	13228				
CTGF-745-13-13230	13230				
CTGF-1230-13-13232	13232				
CTGF-920-13-13234	13234				
CTGF-679-13-13236	13236				
CTGF-992-13-13238	13238				
CTGF-1045-13-13240	13240				
CTGF-1231-13-13242	13242				
CTGF-991-13-13244	13244				
CTGF-998-13-13246	13246				
CTGF-1049-13-13248	13248				

TABLE 2-continued

Antisense backbone, chemistry, and sequence information. o: phosphodiester; s: phosphorothioate; P: 5'phosphorylation; 0: 2'-OH; F: 2'-fluoro; m: 2'O-methyl; +: LNA modification. Capital letters in the sequence signify riobonucleotides, lower case letters signify deoxyribonucleotides.

ID Number	Oligo Number	AntiSense Backbone	AntiSense Chemistry	AntiSense Sequence	SEQ ID NO:
CTGF-1044-13-13250	13250				
CTGF-1327-13-13252	13252				
CTGF-1196-13-13254	13254				
CTGF-562-13-13256	13256				
CTGF-752-13-13258	13258				
CTGF-994-13-13260	13260				
CTGF-1040-13-13262	13262				
CTGF-1984-13-13264	13264				
CTGF-2195-13-13266	13266				
CTGF-2043-13-13268	13268				
CTGF-1892-13-13270	13270				
CTGF-1567-13-13272	13272				
CTGF-1780-13-13274	13274				
CTGF-2162-13-13276	13276				
CTGF-1034-13-13278	13278				
CTGF-2264-13-13280	13280				
CTGF-1032-13-13282	13282				
CTGF-1535-13-13284	13284				
CTGF-1694-13-13286	13286				
CTGF-1588-13-13288	13288				
CTGF-928-13-13290	13290				
CTGF-1133-13-13292	13292				
CTGF-912-13-13294	13294				
CTGF-753-13-13296	13296				

TABLE 2-continued

Antisense backbone, chemistry, and sequence information. o: phosphodiester; s: phosphorothioate; P: 5'phosphorylation; 0: 2'-OH; F: 2'-fluoro; m: 2'O-methyl; +: LNA modification. Capital letters in the sequence signify riobonucleotides, lower case letters signify deoxyribonucleotides.

ID Number	Oligo Number	AntiSense Backbone	AntiSense Chemistry	AntiSense Sequence	SEQ ID NO:
CTGF-918-13-13298	13298				
CTGF-744-13-13300	13300				
CTGF-466-13-13302	13302				
CTGF-917-13-13304	13304				
CTGF-1038-13-13306	13306				
CTGF-1048-13-13308	13308				
CTGF-1235-13-13310	13310				
CTGF-868-13-13312	13312				
CTGF-1131-13-13314	13314				
CTGF-1043-13-13316	13316				
CTGF-751-13-13318	13318				
CTGF-1227-13-13320	13320				
CTGF-867-13-13322	13322				
CTGF-1128-13-13324	13324				
CTGF-756-13-13326	13326				
CTGF-1234-13-13328	13328				
CTGF-916-13-13330	13330				
CTGF-925-13-13332	13332				
CTGF-1225-13-13334	13334				
CTGF-445-13-13336	13336				
CTGF-446-13-13338	13338				
CTGF-913-13-13340	13340				
CTGF-997-13-13342	13342				
CTGF-277-13-13344	13344				

TABLE 2-continued

Antisense backbone, chemistry, and sequence information. o: phosphodiester; s: phosphorothioate; P: 5'phosphorylation; 0: 2'-OH; F: 2'-fluoro; m: 2'O-methyl; +: LNA modification. Capital letters in the sequence signify riobonucleotides, lower case letters signify deoxyribonucleotides.

ID Number	Oligo Number	AntiSense Backbone	AntiSense Chemistry	AntiSense Sequence	SEQ ID NO:
CTGF-1052-13-13346	13346				
CTGF-887-13-13348	13348				
CTGF-914-13-13350	13350				
CTGF-1039-13-13352	13352				
CTGF-754-13-13354	13354				
CTGF-1130-13-13356	13356				
CTGF-919-13-13358	13358				
CTGF-922-13-13360	13360				
CTGF-746-13-13362	13362				
CTGF-993-13-13364	13364				
CTGF-825-13-13366	13366				
CTGF-926-13-13368	13368				
CTGF-923-13-13370	13370				
CTGF-866-13-13372	13372				
CTGF-563-13-13374	13374				
CTGF-823-13-13376	13376				
CTGF-1233-13-13378	13378				
CTGF-924-13-13380	13380				
CTGF-921-13-13382	13382				
CTGF-443-13-13384	13384				
CTGF-1041-13-13386	13386				
CTGF-1042-13-13388	13388				
CTGF-755-13-13390	13390				
CTGF-467-13-13392	13392				

TABLE 2-continued

Antisense backbone, chemistry, and sequence information. o: phosphodiester; s: phosphorothioate; P: 5'phosphorylation; 0: 2'-OH; F: 2'-fluoro; m: 2'O-methyl; +: LNA modification. Capital letters in the sequence signify riobonucleotides, lower case letters signify deoxyribonucleotides.

ID Number	Oligo Number	AntiSense Backbone	AntiSense Chemistry	AntiSense Sequence	SEQ ID NO:
CTGF-995-13-13394	13394				
CTGF-927-13-13396	13396				
SPP1-1025-13-13398	13398				
SPP1-1049-13-13400	13400				
SPP1-1051-13-13402	13402				
SPP1-1048-13-13404	13404				
SPP1-1050-13-13406	13406				
SPP1-1047-13-13408	13408				
SPP1-800-13-13410	13410				
SPP1-492-13-13412	13412				
SPP1-612-13-13414	13414				
SPP1-481-13-13416	13416				
SPP1-614-13-13418	13418				
SPP1-951-13-13420	13420				
SPP1-482-13-13422	13422				
SPP1-856-13-13424	13424				
SPP1-857-13-13426	13426				
SPP1-365-13-13428	13428				
SPP1-359-13-13430	13430				
SPP1-357-13-13432	13432				
SPP1-858-13-13434	13434				
SPP1-1012-13-13436	13436				
SPP1-1014-13-13438	13438				
SPP1-356-13-13440	13440				

TABLE 2-continued

Antisense backbone, chemistry, and sequence information. o: phosphodiester; s: phosphorothioate; P: 5'phosphorylation; 0: 2'-OH; F: 2'-fluoro; m: 2'O-methyl; +: LNA modification. Capital letters in the sequence signify riobonucleotides, lower case letters signify deoxyribonucleotides.

ID Number	Oligo Number	AntiSense Backbone	AntiSense Chemistry	AntiSense Sequence	SEQ ID NO:
SPP1-368-13-13442	13442				
SPP1-1011-13-13444	13444				
SPP1-754-13-13446	13446				
SPP1-1021-13-13448	13448				
SPP1-1330-13-13450	13450				
SPP1-346-13-13452	13452				
SPP1-869-13-13454	13454				
SPP1-701-13-13456	13456				
SPP1-896-13-13458	13458				
SPP1-1035-13-13460	13460				
SPP1-1170-13-13462	13462				
SPP1-1282-13-13464	13464				
SPP1-1537-13-13466	13466				
SPP1-692-13-13468	13468				
SPP1-840-13-13470	13470				
SPP1-1163-13-13472	13472				
SPP1-789-13-13474	13474				
SPP1-841-13-13476	13476				
SPP1-852-13-13478	13478				
SPP1-209-13-13480	13480				
SPP1-1276-13-13482	13482				
SPP1-137-13-13484	13484				
SPP1-711-13-13486	13486				
SPP1-582-13-13488	13488				

TABLE 2-continued

Antisense backbone, chemistry, and sequence information. o: phosphodiester; s: phosphorothioate; P: 5'phosphorylation; 0: 2'-OH; F: 2'-fluoro; m: 2'O-methyl; +: LNA modification. Capital letters in the sequence signify riobonucleotides, lower case letters signify deoxyribonucleotides.

ID Number	Oligo Number	AntiSense Backbone	AntiSense Chemistry	AntiSense Sequence	SEQ ID NO:
SPP1-839-13-13490	13490				
SPP1-1091-13-13492	13492				
SPP1-884-13-13494	13494				
SPP1-903-13-13496	13496				
SPP1-1090-13-13498	13498				
SPP1-474-13-13500	13500				
SPP1-575-13-13502	13502				
SPP1-671-13-13504	13504				
SPP1-924-13-13506	13506				
SPP1-1185-13-13508	13508				
SPP1-1221-13-13510	13510				
SPP1-347-13-13512	13512				
SPP1-634-13-13514	13514				
SPP1-877-13-13516	13516				
SPP1-1033-13-13518	13518				
SPP1-714-13-13520	13520				
SPP1-791-13-13522	13522				
SPP1-813-13-13524	13524				
SPP1-939-13-13526	13526				
SPP1-1161-13-13528	13528				
SPP1-1164-13-13530	13530				
SPP1-1190-13-13532	13532				
SPP1-1333-13-13534	13534				
SPP1-537-13-13536	13536				

TABLE 2-continued

Antisense backbone, chemistry, and sequence information. o: phosphodiester; s: phosphorothioate; P: 5'phosphorylation; 0: 2'-OH; F: 2'-fluoro; m: 2'O-methyl; +: LNA modification. Capital letters in the sequence signify riobonucleotides, lower case letters signify deoxyribonucleotides.

ID Number	Oligo Number	AntiSense Backbone	AntiSense Chemistry	AntiSense Sequence	SEQ ID NO:
SPP1-684-13-13538	13538				
SPP1-707-13-13540	13540				
SPP1-799-13-13542	13542				
SPP1-853-13-13544	13544				
SPP1-888-13-13546	13546				
SPP1-1194-13-13548	13548				
SPP1-1279-13-13550	13550				
SPP1-1300-13-13552	13552				
SPP1-1510-13-13554	13554				
SPP1-1543-13-13556	13556				
SPP1-434-13-13558	13558				
SPP1-600-13-13560	13560				
SPP1-863-13-13562	13562				
SPP1-902-13-13564	13564				
SPP1-921-13-13566	13566				
SPP1-154-13-13568	13568				
SPP1-217-13-13570	13570				
SPP1-816-13-13572	13572				
SPP1-882-13-13574	13574				
SPP1-932-13-13576	13576				
SPP1-1509-13-13578	13578				
SPP1-157-13-13580	13580				
SPP1-350-13-13582	13582				
SPP1-511-13-13584	13584				

TABLE 2-continued

Antisense backbone, chemistry, and sequence information. o: phosphodiester; s: phosphorothioate; P: 5'phosphorylation; 0: 2'-OH; F: 2'-fluoro; m: 2'O-methyl; +: LNA modification. Capital letters in the sequence signify riobonucleotides, lower case letters signify deoxyribonucleotides.

ID Number	Oligo Number	AntiSense Backbone	AntiSense Chemistry	AntiSense Sequence	SEQ ID NO:
SPP1-605-13-13586	13586				
SPP1-811-13-13588	13588				
SPP1-892-13-13590	13590				
SPP1-922-13-13592	13592				
SPP1-1169-13-13594	13594				
SPP1-1182-13-13596	13596				
SPP1-1539-13-13598	13598				
SPP1-1541-13-13600	13600				
SPP1-427-13-13602	13602				
SPP1-533-13-13604	13604				
APOB--13-13763	13763				
APOB--13-13764	13764				
MAP4K4--16-13766	13766	ooooooooooooossssso	Pm000fffff0m0000mmm0	UAGACUUCCACAGAACUCU	49
PPIB--13-13767	13767				
PPIB--15-13768	13768				
PPIB--17-13769	13769				
MAP4K4--16-13939	13939	ooooooooooooossssso	m000f0ffff0m0m00m0m	UAGACAUCCUACACAGCAC	50
APOB-4314-16-13940	13940	ooooooooooooossssso	Pm0fffffff000mmmmm00	UGUUUCUCCAGAUCCUUGC	51
APOB-4314-17-13941	13941	ooooooooooooossssso	Pm0fffffff000mmmmm00	UGUUUCUCCAGAUCCUUGC	52
APOB--16-13942	13942	ooooooooooooossssso	Pm00f000f000mmm0mmm0	UAGCAGAUGAGUCCAUUUG	53
APOB--18-13943	13943	ooooooooooooooooosssssssso	Pm00f000f000mmm0mmm00000	UAGCAGAUGAGUCCAUUUGGAGA	54
APOB--17-13944	13944	ooooooooooooossssso	Pm00f000f000mmm0mmm0	UAGCAGAUGAGUCCAUUUG	55
APOB--19-13945	13945	ooooooooooooooooosssssssso	Pm00f000f000mmm0mmm00000	UAGCAGAUGAGUCCAUUUGGAGA	56
APOB-4314-16-13946	13946	ooooooooooooossssso	Pmf0ff0ffffmmm000mm0	AUGUUGUUUCUCCAGAUCC	57

TABLE 2-continued

Antisense backbone, chemistry, and sequence information. o: phosphodiester; s: phosphorothioate; P: 5'phosphorylation; 0: 2'-OH; F: 2'-fluoro; m: 2'O-methyl; +: LNA modification. Capital letters in the sequence signify riobonucleotides, lower case letters signify deoxyribonucleotides.

ID Number	Oligo Number	AntiSense Backbone	AntiSense Chemistry	AntiSense Sequence	SEQ ID NO:
APOB-4314-17-13947	13947	oooooooooooooSssssso	Pmf0ff0ffffmmm000mm0	AUGUUGUUUCUCCAGAUCC	58
APOB--16-13948	13948	oooooooooooosssssso	Pm0fff000000mmmm0m00	UGUUUGAGGGACUCUGUGA	59
APOB--17-13949	13949	oooooooooooosssssso	Pm0fff000000mmmm0m00	UGUUUGAGGGACUCUGUGA	60
APOB--16-13950	13950	oooooooooooosssssso	Pmff00f0fff00m0m00m0	AUUGGUAUUCAGUGUGAUG	61
APOB--18-13951	13951	ooooooooooooooooosssssso	Pmff00f0fff00m0m00m00m00	AUUGGUAUUCAGUGUGAUGACAC	62
APOB--17-13952	13952	oooooooooooosssssso	Pmff00f0fff00m0m00m0	AUUGGUAUUCAGUGUGAUG	63
APOB--19-13953	13953	ooooooooooooooooosssssso	Pmff00f0fff00m0m00m00m00	AUUGGUAUUCAGUGUGAUGACAC	64
MAP4K4--16-13766.2	13766.2	oooooooooooosssssso	Pm000fffff0m0000mmm0	UAGACUUCCACAGAACUCU	65
CTGF-1222-16-13980	13980	oooooooooooosssssso	Pm0f0fffffm0m00m0m0	UACAUCUUCCUGUAGUACA	66
CTGF-813-16-13981	13981	oooooooooooosssssso	Pm0f0ffff0mmmm0m000	AGGCGCUCCACUCUGUGGU	67
CTGF-747-16-13982	13982	oooooooooooosssssso	Pm0ffffff00mm0m0000	UGUCUUCCAGUCGGUAAGC	68
CTGF-817-16-13983	13983	oooooooooooosssssso	Pm00f000f0fmmm0mmmm0	GAACAGGCGCUCCACUCUG	69
CTGF-1174-16-13984	13984	oooooooooooosssssso	Pm00ff0f00f00m000m00	CAGUUGUAAUGGCAGGCAC	70
CTGF-1005-16-13985	13985	oooooooooooosssssso	Pmff000000mmm000mm0	AGCCAGAAAGCUCAAACUU	71
CTGF-814-16-13986	13986	oooooooooooosssssso	Pm000f0ffff0mmmm0m00	CAGGCGCUCCACUCUGUGG	72
CTGF-816-16-13987	13987	oooooooooooosssssso	Pm0f000f0ffmm0mmmm00	AACAGGCGCUCCACUCUGU	73
CTGF-1001-16-13988	13988	oooooooooooosssssso	Pm0000fff000mmm00m0	AGAAAGCUCAAACUUGAUA	74
CTGF-1173-16-13989	13989	oooooooooooosssssso	Pmff0f00f00m000m0m0	AGUUGUAAUGGCAGGCACA	75
CTGF-749-16-13990	13990	oooooooooooosssssso	Pmf0ffffff00mm00m00	CGUGUCUUCCAGUCGGUAA	76
CTGF-792-16-13991	13991	oooooooooooosssssso	Pm00ff000f00mm00mmm0	GGACCAGGCAGUUGGCUCU	77
CTGF-1162-16-13992	13992	oooooooooooosssssso	Pm000f0f000mmmm00m00	CAGGCACAGGUCUUGAUGA	78
CTGF-811-16-13993	13993	oooooooooooosssssso	Pmf0ffff0ffmm0m00mm0	GCGCUCCACUCUGUGGUCU	79
CTGF-797-16-13994	13994	oooooooooooosssssso	Pm0fff000ff000m00mm0	GGUCUGGACCAGGCAGUUG	80
CTGF-1175-16-13995	13995	oooooooooooosssssso	Pmf00ff0f00m00m000m0	ACAGUUGUAAUGGCAGGCA	81

TABLE 2-continued

Antisense backbone, chemistry, and sequence information. o: phosphodiester; s: phosphorothioate; P: 5'phosphorylation; 0: 2'-OH; F: 2'-fluoro; m: 2'O-methyl; +: LNA modification. Capital letters in the sequence signify riobonucleotides, lower case letters signify deoxyribonucleotides.

ID Number	Oligo Number	AntiSense Backbone	AntiSense Chemistry	AntiSense Sequence	SEQ ID NO:
CTGF-1172-16-13996	13996	ooooooooooooosssssso	Pmff0f00f00m000m0m00	GUUGUAAUGGCAGGCACAG	82
CTGF-1177-16-13997	13997	ooooooooooooosssssso	Pm00f00ff0f00m00m000	GGACAGUUGUAAUGGCAGG	83
CTGF-1176-16-13998	13998	ooooooooooooosssssso	Pm0f00ff0f00m00m0000	GACAGUUGUAAUGGCAGGC	84
CTGF-812-16-13999	13999	ooooooooooooosssssso	Pm0f0ffff0fmmm0m00m0	GGCGCUCCACUCUGUGGUC	85
CTGF-745-16-14000	14000	ooooooooooooosssssso	Pmfffff00ff00m000mm0	UCUUCCAGUCGGUAAGCCG	86
CTGF-1230-16-14001	14001	ooooooooooooosssssso	Pm0fffff0f0m0mmmmmm0	UGUCUCCGUACAUCUUCCU	87
CTGF-920-16-14002	14002	ooooooooooooosssssso	Pmffff0f0000mmm00m0	AGCUUCGCAAGGCCUGACC	88
CTGF-679-16-14003	14003	ooooooooooooosssssso	Pm0ffffff0f00m0mmmm0	CACUCCUCGCAGCAUUUCC	89
CTGF-992-16-14004	14004	ooooooooooooosssssso	Pm00fff00f000mmm0000	AAACUUGAUAGGCUUGGAG	90
CTGF-1045-16-14005	14005	ooooooooooooosssssso	Pmffff0f0000mmm00mm0	ACUCCACAGAAUUUAGCUC	91
CTGF-1231-16-14006	14006	ooooooooooooosssssso	Pmf0fffff0f0m0mmmmm0	AUGUCUCCGUACAUCUUCC	92
CTGF-991-16-14007	14007	ooooooooooooosssssso	Pm0fff00f000mmm00000	AACUUGAUAGGCUUGGAGA	93
CTGF-998-16-14008	14008	ooooooooooooosssssso	Pm00fff000fmm00m0000	AAGCUCAAACUUGAUAGGC	94
CTGF-1049-16-14009	14009	ooooooooooooosssssso	Pmf0f0ffff0m0000mmm0	ACAUACUCCACAGAAUUUA	95
CTGF-1044-16-14010	14010	ooooooooooooosssssso	Pmfff0f0000mmm00mmm0	CUCCACAGAAUUUAGCUCG	96
CTGF-1327-16-14011	14011	ooooooooooooosssssso	Pm0f0ff0ff0000mm0mm0	UGUGCUACUGAAAUCAUUU	97
CTGF-1196-16-14012	14012	ooooooooooooosssssso	Pm0000f0ff0mm0mmmmm0	AAAGAUGUCAUUGUCUCCG	98
CTGF-562-16-14013	14013	ooooooooooooosssssso	Pmf0f0ff00f0mmm0m000	GUGCACUGGUACUUGCAGC	99
CTGF-752-16-14014	14014	ooooooooooooosssssso	Pm00f0f0fffmmm00mm00	AAACGUGUCUUCCAGUCGG	100
CTGF-994-16-14015	14015	ooooooooooooosssssso	Pmf000fff00m000mmm00	UCAAACUUGAUAGGCUUGG	101
CTGF-1040-16-14016	14016	ooooooooooooosssssso	Pmf0000fff00mmm00m00	ACAGAAUUUAGCUCGGUAU	102
CTGF-1984-16-14017	14017	ooooooooooooosssssso	Pmf0f0ffff0mmm0m00m0	UUACAUUCUACCUAUGGUG	103
CTGF-2195-16-14018	14018	ooooooooooooosssssso	Pm00ff00ff00mm0m0m00	AAACUGAUCAGCUAUAUAG	104
CTGF-2043-16-14019	14019	ooooooooooooosssssso	Pm0fff000f0000mmmmm0	UAUCUGAGCAGAAUUUCCA	105

TABLE 2-continued

Antisense backbone, chemistry, and sequence information. o: phosphodiester; s: phosphorothioate; P: 5'phosphorylation; 0: 2'-OH; F: 2'-fluoro; m: 2'O-methyl; +: LNA modification. Capital letters in the sequence signify riobonucleotides, lower case letters signify deoxyribonucleotides.

ID Number	Oligo Number	AntiSense Backbone	AntiSense Chemistry	AntiSense Sequence	SEQ ID NO:
CTGF-1892-16-14020	14020	ooooooooooooossssso	Pmf00fff000m00mm0m00	UUAACUUAGAUAACUGUAC	106
CTGF-1567-16-14021	14021	ooooooooooooossssso	Pm0ff0fff0f0m0000m00	UAUUACUCGUAUAAGAUGC	107
CTGF-1780-16-14022	14022	ooooooooooooossssso	Pm0ff0fff00mmm00mm0	AAGCUGUCCAGUCUAAUCG	108
CTGF-2162-16-14023	14023	ooooooooooooossssso	Pm00f00000fm0mmm0mm0	UAAUAAAGGCCAUUUGUUC	109
CTGF-1034-16-14024	14024	ooooooooooooossssso	Pmff00fff00m0m0mmmm0	UUUAGCUCGGUAUGUCUUC	110
CTGF-2264-16-14025	14025	ooooooooooooossssso	Pmf0ffff00m000m0000	ACACUCUCAACAAAUAAAC	111
CTGF-1032-16-14026	14026	ooooooooooooossssso	Pm00fff00f0m0mmmmm00	UAGCUCGGUAUGUCUUCAU	112
CTGF-1535-16-14027	14027	ooooooooooooossssso	Pm00ffffff0mm00m0m0	UAACCUUUCUGCUGGUACC	113
CTGF-1694-16-14028	14028	ooooooooooooossssso	Pmf000000f00mmm00mm0	UUAAGGAACAACUUGACUC	114
CTGF-1588-16-14029	14029	ooooooooooooossssso	Pmf0f0ffff000m00m000	UUACACUUCAAAUAGCAGG	115
CTGF-928-16-14030	14030	ooooooooooooossssso	Pmff000ff00mmmm0m000	UCCAGGUCAGCUUCGCAAG	116
CTGF-1133-16-14031	14031	ooooooooooooossssso	Pmfffff0f00mmmm0mm0	CUUCUUCAUGACCUCGCCG	117
CTGF-912-16-14032	14032	ooooooooooooossssso	Pm000fff00fm0m0m0m00	AAGGCCUGACCAUGCACAG	118
CTGF-753-16-14033	14033	ooooooooooooossssso	Pm000f0f0ffmmmm00mm0	CAAACGUGUCUUCCAGUCG	119
CTGF-918-16-14034	14034	ooooooooooooossssso	Pmfff0f0000mmm00mm00	CUUCGCAAGGCCUGACCAU	120
CTGF-744-16-14035	14035	ooooooooooooossssso	Pmffff00ff00m000mm00	CUUCCAGUCGGUAAGCCGC	121
CTGF-466-16-14036	14036	ooooooooooooossssso	Pmf00ffff0f00mm00mm0	CCGAUCUUGCGGUUGGCCG	122
CTGF-917-16-14037	14037	ooooooooooooossssso	Pmff0f0000fmm00mm0m0	UUCGCAAGGCCUGACCAUG	123
CTGF-1038-16-14038	14038	ooooooooooooossssso	Pm00fff00fmm0m0m00	AGAAUUUAGCUCGGUAUGU	124
CTGF-1048-16-14039	14039	ooooooooooooossssso	Pm0f0ffff0f0000mmm00	CAUACUCCACAGAAUUUAG	125
CTGF-1235-16-14040	14040	ooooooooooooossssso	Pm0ff0f0fffmmm0m0m0	UGCCAUGUCUCCGUACAUC	126
CTGF-868-16-14041	14041	ooooooooooooossssso	Pm000f0ff0fm0mm00m00	GAGGCGUUGUCAUUGGUAA	127
CTGF-1131-16-14042	14042	ooooooooooooossssso	Pmffff0f00fmmm0mm0m0	UCUUCAUGACCUCGCCGUC	128
CTGF-1043-16-14043	14043	ooooooooooooossssso	Pmff0f0000fmm00mmm00	UCCACAGAAUUUAGCUCGG	129

TABLE 2-continued

Antisense backbone, chemistry, and sequence information. o: phosphodiester; s: phosphorothioate; P: 5'phosphorylation; 0: 2'-OH; F: 2'-fluoro; m: 2'O-methyl; +: LNA modification. Capital letters in the sequence signify riobonucleotides, lower case letters signify deoxyribonucleotides.

ID Number	Oligo Number	AntiSense Backbone	AntiSense Chemistry	AntiSense Sequence	SEQ ID NO:
CTGF-751-16-14044	14044	oooooooooooooosssssso	Pm0f0f0ffffmm00mm000	AACGUGUCUUCCAGUCGGU	130
CTGF-1227-16-14045	14045	oooooooooooooosssssso	Pmfff0f0f0fmmmmmm0m0	CUCCGUACAUCUUCCUGUA	131
CTGF-867-16-14046	14046	oooooooooooooosssssso	Pm0f0ff0ff0mm00m000	AGGCGUUGUCAUUGGUAAC	132
CTGF-1128-16-14047	14047	oooooooooooooosssssso	Pmf0f00ffff0mm0mm000	UCAUGACCUCGCCGUCAGG	133
CTGF-756-16-14048	14048	oooooooooooooosssssso	Pm0ff000f0f0mmmmmm00	GGCCAAACGUGUCUUCCAG	134
CTGF-1234-16-14049	14049	oooooooooooooosssssso	Pmff0f0ffffmm0m0mm0	GCCAUGUCUCCGUACAUCU	135
CTGF-916-16-14050	14050	oooooooooooooosssssso	Pmf0f0000ffm00mm0m00	UCGCAAGGCCUGACCAUGC	136
CTGF-925-16-14051	14051	oooooooooooooosssssso	Pm0ff00fffmm0000m0	AGGUCAGCUUCGCAAGGCC	137
CTGF-1225-16-14052	14052	oooooooooooooosssssso	Pmf0f0f0fffmmmm0m000	CCGUACAUCUUCCUGUAGU	138
CTGF-445-16-14053	14053	oooooooooooooosssssso	Pm00ff0000fm0m000000	GAGCCGAAGUCACAGAAGA	139
CTGF-446-16-14054	14054	oooooooooooooosssssso	Pm000ff0000mm0m00000	GGAGCCGAAGUCACAGAAG	140
CTGF-913-16-14055	14055	oooooooooooooosssssso	Pm0000fff00mm0m0m0m0	CAAGGCCUGACCAUGCACA	141
CTGF-997-16-14056	14056	oooooooooooooosssssso	Pmfff000ffm00m000m0	AGCUCAAACUUGAUAGGCU	142
CTGF-277-16-14057	14057	oooooooooooooosssssso	Pmf0f00ffff00mm00m00	CUGCAGUUCUGGCCGACGG	143
CTGF-1052-16-14058	14058	oooooooooooooosssssso	Pm0f0f0f0ffmm0m00000	GGUACAUACUCCACAGAAU	144
CTGF-887-16-14059	14059	oooooooooooooosssssso	Pmf0ffffff00mmm0m00	CUGCUUCUCUAGCCUGCAG	145
CTGF-914-16-14060	14060	oooooooooooooosssssso	Pmf0000fff00mm0m0m00	GCAAGGCCUGACCAUGCAC	146
CTGF-1039-16-14061	14061	oooooooooooooosssssso	Pm0000fff00mmm00m0m0	CAGAAUUUAGCUCGGUAUG	147
CTGF-754-16-14062	14062	oooooooooooooosssssso	Pmf000f0f0fmmmmm00m0	CCAAACGUGUCUUCCAGUC	148
CTGF-1130-16-14063	14063	oooooooooooooosssssso	Pmfff0f00ffmmmm0mm0	CUUCAUGACCUCGCCGUCA	149
CTGF-919-16-14064	14064	oooooooooooooosssssso	Pmffff0f0000mmm00mm0	GCUUCGCAAGGCCUGACCA	150
CTGF-922-16-14065	14065	oooooooooooooosssssso	Pmf00ffff0f0000mmm00	UCAGCUUCGCAAGGCCUGA	151
CTGF-746-16-14066	14066	oooooooooooooosssssso	Pmfffff00fm0m000m0	GUCUUCCAGUCGGUAAGCC	152
CTGF-993-16-14067	14067	oooooooooooooosssssso	Pm000fff00f000mmm000	CAAACUUGAUAGGCUUGGA	153

TABLE 2-continued

Antisense backbone, chemistry, and sequence information. o: phosphodiester; s: phosphorothioate; P: 5'phosphorylation; 0: 2'-OH; F: 2'-fluoro; m: 2'O-methyl; +: LNA modification. Capital letters in the sequence signify riobonucleotides, lower case letters signify deoxyribonucleotides.

ID Number	Oligo Number	AntiSense Backbone	AntiSense Chemistry	AntiSense Sequence	SEQ ID NO:
CTGF-825-16-14068	14068	ooooooooooooossssso	Pm0ffff0000m000m0m0	AGGUCUUGGAACAGGCGCU	154
CTGF-926-16-14069	14069	ooooooooooooossssso	Pm000ff00ffmmm00000	CAGGUCAGCUUCGCAAGGC	155
CTGF-923-16-14070	14070	ooooooooooooossssso	Pmff00ffff0m0000mmm0	GUCAGCUUCGCAAGGCCUG	156
CTGF-866-16-14071	14071	ooooooooooooossssso	Pm0f0ff0ff0mm00m00m0	GGCGUUGUCAUUGGUAACC	157
CTGF-563-16-14072	14072	ooooooooooooossssso	Pmf0f0ff00m0mmm0m00	CGUGCACUGGUACUUGCAG	158
CTGF-823-16-14073	14073	ooooooooooooossssso	Pmffff0000f000m0mmm0	GUCUUGGAACAGGCGCUCC	159
CTGF-1233-16-14074	14074	ooooooooooooossssso	Pmf0f0ffff0m0m0mmm0	CCAUGUCUCCGUACAUCUU	160
CTGF-924-16-14075	14075	ooooooooooooossssso	Pm0ff00ffff0m0000mm0	GGUCAGCUUCGCAAGGCCU	161
CTGF-921-16-14076	14076	ooooooooooooossssso	Pm00ffff0f0000mmm000	CAGCUUCGCAAGGCCUGAC	162
CTGF-443-16-14077	14077	ooooooooooooossssso	Pmff0000ff0m00000000	GCCGAAGUCACAGAAGAGG	163
CTGF-1041-16-14078	14078	ooooooooooooossssso	Pm0f0000fff00mmm00m0	CACAGAAUUUAGCUCGGUA	164
CTGF-1042-16-14079	14079	ooooooooooooossssso	Pmf0f0000ffm00mmm000	CCACAGAAUUUAGCUCGGU	165
CTGF-755-16-14080	14080	ooooooooooooossssso	Pmff000f0f0mmmmmm000	GCCAAACGUGUCUUCCAGU	166
CTGF-467-16-14081	14081	ooooooooooooossssso	Pmf0f00ffff0m0mm00m0	GCCGAUCUUGCGGUUGGCC	167
CTGF-995-16-14082	14082	ooooooooooooossssso	Pmff000fff00m000mmm0	CUCAAACUUGAUAGGCUUG	168
CTGF-927-16-14083	14083	ooooooooooooossssso	Pmf000ff00fmmm0m0000	CCAGGUCAGCUUCGCAAGG	169
SPP1-1091-16-14131	14131	ooooooooooooossssso	Pmff00ff000m0m0000m0	UUUGACUAAAUGCAAAGUG	170
PPIB--16-14188	14188	oooooooooooooossssss	Pm0fffff0f00mm000mm0	UGUUUUUGUAGCCAAAUCC	171
PPIB--17-14189	14189	oooooooooooooossssss	Pm0fffff0f00mm000mm0	UGUUUUUGUAGCCAAAUCC	172
PPIB--18-14190	14190	oooooooooooooossssss	Pm0fffff0f00mm000mm0	UGUUUUUGUAGCCAAAUCC	173
pGL3-1172-16-14386	14386	ooooooooooooossssso	Pm00ff0f0ffm0mm00mm0	AAAUCGUAUUUGUCAAUCA	174
pGL3-1172-16-14387	14387	ooooooooooooossssso	Pm00ff0f0ffm0mm00mm0	AAAUCGUAUUUGUCAAUCA	175
MAP4K4-2931-25-14390	14390				

TABLE 2-continued

Antisense backbone, chemistry, and sequence information. o: phosphodiester; s: phosphorothioate; P: 5'phosphorylation; 0: 2'-OH; F: 2'-fluoro; m: 2'O-methyl; +: LNA modification. Capital letters in the sequence signify riobonucleotides, lower case letters signify deoxyribonucleotides.

ID Number	Oligo Number	AntiSense Backbone	AntiSense Chemistry	AntiSense Sequence	SEQ ID NO:
miR-122--23-14391	14391				
	14084	ooooooooooooossssso	Pmff00fff0f000000m00	UCUAAUUCAUGAGAAAUAC	616
	14085	ooooooooooooossssso	Pm00ff00fffm000000m0	UAAUUGACCUCAGAAGAUG	617
	14086	ooooooooooooossssso	Pmff00ff00fmmm000000	UUUAAUUGACCUCAGAAGA	618
	14087	ooooooooooooossssso	Pm0ff00ffff000000m00	AAUUGACCUCAGAAGAUGC	619
	14088	ooooooooooooossssso	Pmf00ff00ffmm0000000	UUAAUUGACCUCAGAAGAU	620
	14089	ooooooooooooossssso	Pmff00ffff000000m0m0	AUUGACCUCAGAAGAUGCA	621
	14090	ooooooooooooossssso	Pmf0fff00ff00mmm0mm0	UCAUCCAGCUGACUCGUUU	622
	14091	ooooooooooooossssso	Pm0fff0ff0000m00m00	AGAUUCAUCAGAAUGGUGA	623
	14092	ooooooooooooossssso	Pm00ffff00fmm0m000m0	UGACCUCAGUCCAUAAACC	624
	14093	ooooooooooooossssso	Pm0f00f0000mmm0mm000	AAUGGUGAGACUCAUCAGA	625
	14094	ooooooooooooossssso	Pmff00ffff00mmm0m000	UUUGACCUCAGUCCAUAAA	626
	14095	ooooooooooooossssso	Pmff0f00ff0m0000mmm0	UUCAUGGCUGUGAAAUUCA	627
	14096	ooooooooooooossssso	Pm00f00f0000mmm0mm00	GAAUGGUGAGACUCAUCAG	628
	14097	ooooooooooooossssso	Pm00fffff0mmm0m0m00	UGGCUUUCCGCUUAUAUAA	629
	14098	ooooooooooooossssso	Pmf00fffff0mmm0m0m0	UUGGCUUUCCGCUUAUAUA	630
	14099	ooooooooooooossssso	Pmf0fff0f0f00mm0m000	UCAUCCAUGUGGUCAUGGC	631
	14100	ooooooooooooossssso	Pmf0f00ff0f00mmmmm00	AUGUGGUCAUGGCUUUCGU	632
	14101	ooooooooooooossssso	Pmf00ff0f00mmmmm0mm0	GUGGUCAUGGCUUUCGUUG	633
	14102	ooooooooooooossssso	Pmff00ffffmmmm0m00	AUUGGCUUUCCGCUUAUAU	634
	14103	ooooooooooooossssso	Pm00f0f0000mmmm000m0	AAAUACGAAAUUUCAGGUG	635
	14104	ooooooooooooossssso	Pm000f0f0000mmmm000	AGAAAUACGAAAUUUCAGG	636
	14105	ooooooooooooossssso	Pm00ff0f00fmmmm0mm00	UGGUCAUGGCUUUCGUUGG	637
	14106	ooooooooooooossssso	Pmf0ff0fff0m0m00mm00	AUAUCAUCCAUGUGGUCAU	638

TABLE 2-continued

Antisense backbone, chemistry, and sequence information. o: phosphodiester; s: phosphorothioate; P: 5'phosphorylation; 0: 2'-OH; F: 2'-fluoro; m: 2'O-methyl; +: LNA modification. Capital letters in the sequence signify riobonucleotides, lower case letters signify deoxyribonucleotides.

ID Number	Oligo Number	AntiSense Backbone	AntiSense Chemistry	AntiSense Sequence	SEQ ID NO:
	14107	ooooooooooooos ssssso	Pm0f0f0000fmmm 000m00	AAUACGAAAUUUCAGGU GU	639
	14108	ooooooooooooos ssssso	Pm0ff000000mm0 mmm00	AAUCAGAAGGCGCGUUC AG	640
	14109	ooooooooooooos ssssso	Pmfff0f000000m 0m0000	AUUCAUGAGAAAUACGA AA	641
	14110	ooooooooooooos ssssso	Pmf0fff0f00000 00m000	CUAUUCAUGAGAGAAUA AC	642
	14111	ooooooooooooos ssssso	Pmfff0ff000mmm 0mmm00	UUUCGUUGGACUUACUU GG	643
	14112	ooooooooooooos ssssso	Pmf0ffff0fm0m m00mm0	UUGCUCUCAUCAUUGGC UU	644
	14113	ooooooooooooos ssssso	Pmff00ffffmmm mmmm0	UUCAACUCCUCGCUUUC CA	645
	14114	ooooooooooooos ssssso	Pm00ff0ff00mm0 m0mm00	UGACUAUCAAUCACAUC GG	646
	14115	ooooooooooooos ssssso	Pm0f0f0ff0mmm0 0mmm0	AGAUGCACUAUCUAAUU CA	647
	14116	ooooooooooooos ssssso	Pm0f000f0f0m0m mm00m0	AAUAGAUACACAUUCAA CC	648
	14117	ooooooooooooos ssssso	Pmfffff0f0000 m000m0	UUCUUCUAUAGAAUGAA CA	649
	14118	ooooooooooooos ssssso	Pm0ff0ff000m00 mm0m00	AAUUGCUGGACAACCGU GG	650
	14119	ooooooooooooos ssssso	Pmf0fffff0m0m 0m0000	UCGCUUUCCAUGUGUGA GG	651
	14120	ooooooooooooos ssssso	Pm00fff000fm0m mm0m00	UAAUCUGGACUGCUUGU GG	652
	14121	ooooooooooooos ssssso	Pmf0f0fff00mm0 0m0000	ACACAUUCAACCAAUAA AC	653
	14122	ooooooooooooos ssssso	Pmfff0ffff0m00 mm0mm0	ACUCGUUUCAUAACUGU CC	654
	14123	ooooooooooooos ssssso	Pmf00fff000mm0 mmm0m0	AUAAUCUGGACUGCUUG UG	655
	14124	ooooooooooooos ssssso	Pmffff0fff0m0m 00mmm0	UUUCCGCUUAUAUAAUC UG	656
	14125	ooooooooooooos ssssso	Pm0fff00ff00m0 m00m00	UGUUUAACUGGUAUGGC AC	657
	14126	ooooooooooooos ssssso	Pm0f0000f000m0 m000m0	UAUAGAAUGAACAUAGA CA	658
	14127	ooooooooooooos ssssso	Pmffffff00fm0m 0mmm0	UUUCCUUGGUCGGCGUU UG	659
	14128	ooooooooooooos ssssso	Pmf0f0f0ff0mmm 00mmm0	GUAUGCACCAUUCAACU CC	660
	14129	ooooooooooooos ssssso	Pmf00ff0ff0m0m 0m0mm0	UCGGCCAUCAUAUGUGU CU	661
	14130	ooooooooooooos ssssso	Pm0fff000ff0mm m0m000	AAUCUGGACUGCUUGUG GC	662

TABLE 2-continued

Antisense backbone, chemistry, and sequence information. o: phosphodiester; s: phosphorothioate; P: 5'phosphorylation; 0: 2'-OH; F: 2'-fluoro; m: 2'O-methyl; +: LNA modification. Capital letters in the sequence signify riobonucleotides, lower case letters signify deoxyribonucleotides.

ID Number	Oligo Number	AntiSense Backbone	AntiSense Chemistry	AntiSense Sequence	SEQ ID NO:
	14132	ooooooooooooos sssssso	Pmf0ff0000f0mm m0mm00	ACAUCGGAAUGCUCAUU GC	663
	14133	ooooooooooooos sssssso	Pm00fffff00mm0 mm00m0	AAGUUCCUGACUAUCAA UC	664
	14134	ooooooooooooos sssssso	Pmf00ff000f0m0 000m00	UUGACUAAAUGCAAAGU GA	665
	14135	ooooooooooooos sssssso	Pm0fff0ff000mm 00m00	AGACUCAUCAGACUGGU GA	666
	14136	ooooooooooooos sssssso	Pmf0f0f0f0fmm0 mm0m00	UCAUAUGUGUCUACUGU GG	667
	14137	ooooooooooooos sssssso	Pmf0fffff0fmm0 m00m00	AUGUCCUCGUCUGUAGC AU	668
	14138	ooooooooooooos sssssso	Pm00fff0f00mm0 0mmmm0	GAAUUCACGGCUGACUU UG	669
	14139	ooooooooooooos sssssso	Pmf0fffff000mm m000m0	UUAUUUCCAGACUCAAA UA	670
	14140	ooooooooooooos sssssso	Pm000ff0f000mm 000mm0	GAAGCCACAAACUAAAC UA	671
	14141	ooooooooooooos sssssso	Pmffff0ff000mm m0mmm0	CUUUCGUUGGACUUACU UG	672
	14142	ooooooooooooos sssssso	Pmfff0f0000mmm mmm000	GUCUGCGAAACUUCUUA GA	673
	14143	ooooooooooooos sssssso	Pm0f0fff0ff0mm mmm0m0	AAUGCUCAUUGCUCUCA UC	674
	14144	ooooooooooooos sssssso	Pmf0f0ff0ffm00 mmm0m0	AUGCACUAUCUAAUUCA UG	675
	14145	ooooooooooooos sssssso	Pmff0f0f0f0mm0 mmm000	CUUGUAUGCACCAUUCA AC	676
	14146	ooooooooooooos sssssso	Pm00fff0fffm0m 00mm00	UGACUCGUUUCAUAACU GU	677
	14147	ooooooooooooos sssssso	Pmff00f0fffm00 mm0mm0	UUCAGCACUCUGGUCAU CC	678
	14148	ooooooooooooos sssssso	Pm00fff0f00mm0 m00000	AAAUUCAUGGCUGUGGA AU	679
	14149	ooooooooooooos sssssso	Pmf0fff00ff00m 000mm0	ACAUUCAACCAAUAAAC UG	680
	14150	ooooooooooooos sssssso	Pm0f0f0fff00mm 00m000	UACACAUUCAACCAAUA AA	681
	14151	ooooooooooooos sssssso	Pmff00ff0ffmmm 000mm0	AUUAGUUAUUUCCAGAC UC	682
	14152	ooooooooooooos sssssso	Pmffff0fff0m00 000000	UUUCUAUUCAUGAGAGA AU	683
	14153	ooooooooooooos sssssso	Pmff00ff0ff00m 000mm0	UUCGGUUGCUGGCAGGU CC	684
	14154	ooooooooooooos sssssso	Pm0f0f0f0000m0 0m0mm0	CAUGUGUGAGGUGAUGU CC	685
	14155	ooooooooooooos sssssso	Pmf0ff0fff00mm mmmm00	GCACCAUUCAACUCCUC GC	686

TABLE 2-continued

Antisense backbone, chemistry, and sequence information. o: phosphodiester; s: phosphorothioate; P: 5'phosphorylation; 0: 2'-OH; F: 2'-fluoro; m: 2'O-methyl; +: LNA modification. Capital letters in the sequence signify riobonucleotides, lower case letters signify deoxyribonucleotides.

ID Number	Oligo Number	AntiSense Backbone	AntiSense Chemistry	AntiSense Sequence	SEQ ID NO:
	14156	ooooooooooooos ssssso	Pm0fff00ff00mm m0mmm0	CAUCCAGCUGACUCGUU UC	687
	14157	ooooooooooooos ssssso	Pmfffff0fff0m0 m00mm0	CUUUCCGCUUAUAUAAU CU	688
	14158	ooooooooooooos ssssso	Pm0ff0f0ff0000 m0mmm0	AAUCACAUCGGAAUGCU CA	689
	14159	ooooooooooooos ssssso	Pmf0f0ff00fm0m mmmm00	ACACAUUAGUUAUUUCC AG	690
	14160	ooooooooooooos ssssso	Pmfff0f0000m00 0m0m00	UUCUAUAGAAUGAACAU AG	691
	14161	ooooooooooooos ssssso	Pm0f00f00f00mm m0m0m0	UACAGUGAUAGUUUGCA UU	692
	14162	ooooooooooooos ssssso	Pmf000f00ff00m 0mm0m0	AUAAGCAAUUGACACCA CC	693
	14163	ooooooooooooos ssssso	Pmff0ff00ff0mm 000m00	UUUAUUAAUUGCUGGAC AA	694
	14164	ooooooooooooos ssssso	Pmf0ff0000fmmm m0000	UCAUCAGAGUCGUUCGA GU	695
	14165	ooooooooooooos ssssso	Pmf000ff0f0mm0 mm0mm0	AUAAACCACACUAUCAC CU	696
	14166	ooooooooooooos ssssso	Pmf0ff0ff00mmm mmm0m0	UCAUCAUUGGCUUUCCG CU	697
	14167	ooooooooooooos ssssso	Pmfffff00fm0mm 00mm0	AGUUCCUGACUAUCAAU CA	698
	14168	ooooooooooooos ssssso	Pmff0f00ff00mm mm0000	UUCACGGCUGACUUUGG AA	699
	14169	ooooooooooooos ssssso	Pmffff0f00f00m 000mm0	UUCUCAUGGUAGUGAGU UU	700
	14170	ooooooooooooos ssssso	Pm0ff00fff0mmm 00mm00	AAUCAGCCUGUUUAACU GG	701
	14171	ooooooooooooos ssssso	Pm0ffff00f0mmm m00mm0	GGUUUCAGCACUCUGGU CA	702
	14172	ooooooooooooos ssssso	Pmff0000f0fmm0 mm0mm0	AUCGGAAUGCUCAUUGC UC	703
	14173	ooooooooooooos ssssso	Pm00ff0f0000mm m0m000	UGGCUGUGGAAUUCACG GC	704
	14174	ooooooooooooos ssssso	Pm000f00ff00m0 mm0mm0	UAAGCAAUUGACACCAC CA	705
	14175	ooooooooooooos ssssso	Pm00fffff0f00m 00m000	CAAUUCUCAUGGUAGUG AG	706
	14176	ooooooooooooos ssssso	Pm00ffff0fm00 0mmm00	UGGCUUUCGUUGGACUU AC	707
	14177	ooooooooooooos ssssso	Pm0ff00f00fm00 mmm0m0	AAUCAGUGACCAGUUCA UC	708
	14178	ooooooooooooos ssssso	Pmfff0f000mm0m 0mm00	AGUCCAUAAACCACACU AU	709
	14179	ooooooooooooos ssssso	Pm00f0fff00mm 0mmm00	CAGCACUCUGGUCAUCC AG	710

TABLE 2-continued

Antisense backbone, chemistry, and sequence information. o: phosphodiester; s: phosphorothioate; P: 5'phosphorylation; 0: 2'-OH; F: 2'-fluoro; m: 2'O-methyl; +: LNA modification. Capital letters in the sequence signify riobonucleotides, lower case letters signify deoxyribonucleotides.

ID Number	Oligo Number	AntiSense Backbone	AntiSense Chemistry	AntiSense Sequence	SEQ ID NO:
	14180	ooooooooooooos ssssso	Pm0ff00ff0f0mm 0000m0	UAUCAAUCACAUCGGAA UG	711
	14181	ooooooooooooos ssssso	Pmfff0f00ff00m mmm000	AUUCACGGCUGACUUUG GA	712
	14182	ooooooooooooos ssssso	Pmf000f0f0f0mm m00mm0	AUAGAUACACAUUCAAC CA	713
	14183	ooooooooooooos ssssso	Pmffff000ffm00 0m0000	UUUCCAGACUCAAAUAG AU	714
	14184	ooooooooooooos ssssso	Pmf00ff0ff000m 00mm00	UUAAUUGCUGGACAACC GU	715
	14185	ooooooooooooos ssssso	Pm0ff00ff0fm00 0m00m0	UAUUAAUUGCUGGACAA CC	716
	14186	ooooooooooooos ssssso	Pmff0fff000mm0 0m000	AGUCGUUCGAGUCAAUG GA	717
	14187	ooooooooooooos ssssso	Pmff0ff00f000m mm0m00	GUUGCUGGCAGGUCCGU GG	718

TABLE 3

Sense backbone, chemistry, and sequence information. o: phosphodiester; s: phosphorothioate; P: 5'phosphorylation; 0: 2'-OH; F: 2'-fluoro; m: 2'O-methyl; +: LNA modification. Capital letters in the sequence signify ribonucleotides, lower case letters signify deoxyribonucleotides.

ID Number	Oligo Number	OHang Sense Chem.	Sense Backbone	Sense Chemistry	Sense Sequence	SEQ ID NO:
APOB-10167-20-12138	**12138**	chl	oooooooooooo ooooooooso	0000000000000 0000000	GUCAUCACACUGA AUACCAAU	176
APOB-10167-20-12139	12139	chl	oooooooooooo ooooooooso	0000000000000 0000000	GUGAUCAGACUCA AUACGAAU	177
MAP4K4-2931-13-12266	12266	chl	oooooooooooss o	mm0m00000mmm0	CUGUGGAAGUCUA	178
MAP4K4-2931-16-12293	12293	chl	oooooooooooss o	mm0m00000mmm0	CUGUGGAAGUCUA	179
MAP4K4-2931-16-12383	12383	chl	oooooooooooo o	mm0m00000mmm0	CUGUGGAAGUCUA	180
MAP4K4-2931-16-12384	12384	chl	oooooooooooo o	mm0m00000mmm0	CUGUGGAAGUCUA	181
MAP4K4-2931-16-12385	12385	chl	oooooooooooo o	mm0m00000mmm0	CUGUGGAAGUCUA	182
MAP4K4-2931-16-12386	12386	chl	oooooooooooss o	0mm0m00000mmm 0	CUGUGGAAGUCUA	183
MAP4K4-2931-16-12387	12387	chl	oooooooooooo o	mm0m00000mmm0	CUGUGGAAGUCUA	184

TABLE 3-continued

Sense backbone, chemistry, and sequence information. o: phosphodiester; s: phosphorothioate; P: 5'phosphorylation; 0: 2'-OH; F: 2'-fluoro; m: 2'O-methyl; +: LNA modification. Capital letters in the sequence signify ribonucleotides, lower case letters signify deoxyribonucleotides.

ID Number	Oligo Number	OHang Sense Chem.	Sense Backbone	Sense Chemistry	Sense Sequence	SEQ ID NO:
MAP4K4-2931-15-12388	12388	chl	oooooooooooo o	mm0m00000mmm0	CUGUGGAAGUCUA	185
MAP4K4-2931-13-12432	12432	chl	oooooooooooo o	DY547mm0m0000 0mmm0	CUGUGGAAGUCUA	186
MAP4K4-2931-13-12266.2	12266.2	chl	oooooooooooos s	mm0m00000mmm0	CUGUGGAAGUCUA	187
APOB--21-12434	12434	chl	oooooooooooo ooooooooso	0000000000000 0000000	GUCAUCACACUGA AUACCAAU	188
APOB--21-12435	12435	chl	oooooooooooo ooooooooso	DY54700000000 000000000000	GUGAUCAGACUCA AUACGAAU	189
MAP4K4-2931-16-12451	12451	chl	oooooooooooos s	0mm0m00000mmm 0	CUGUGGAAGUCUA	190
MAP4K4-2931-16-12452	12452	chl	oooooooooooos s	mm0m00000mmm0	CUGUGGAAGUCUA	191
MAP4K4-2931-16-12453	12453	chl	oooooooooooos s	mm0m00000mmm0	CUGUGGAAGUCUA	192
MAP4K4-2931-17-12454	12454	chl	oooooooooooos s	0mm0m00000mmm 0	CUGUGGAAGUCUA	193
MAP4K4-2931-17-12455	12455	chl	oooooooooooos s	mm0m00000mmm0	CUGUGGAAGUCUA	194
MAP4K4-2931-19-12456	12456	chl	oooooooooooos s	mm0m00000mmm0	CUGUGGAAGUCUA	195
--27-12480	12480	chl	oooooooooooo oooooooooooo sso	DY547mm0f000f 0055f5f00mm00 000m000	UCAUAGGUAACCU CUGGUUGAAAGUG A	196
--27-12481	12481	chl	oooooooooooo oooooooooooo sso	DY547mm05f050 00f05ff0m0000 0000m00	CGGCUACAGGUGC UUAUGAAGAAAGU A	197
APOB-10167-21-12505	12505	chl	oooooooooooo ooooooooos	0000000000000 00000000	GUCAUCACACUGA AUACCAAU	198
APOB-10167-21-12506	12506	chl	oooooooooooo ooooooooos	0000000000000 00000000	GUGAUCAGACUCA AUACGAAU	199
MAP4K4-2931-16-12539	12539	chl	oooooooooooos s	DY547mm0m0000 0mmm0	CUGUGGAAGUCUA	200
APOB-10167-21-12505.2	12505.2	chl	oooooooooooo ooooooooso	0000000000000 0000000	GUCAUCACACUGA AUACCAAU	201
APOB-10167-21-12506.2	12506.2	chl	oooooooooooo ooooooooso	0000000000000 0000000	GUGAUCAGACUCA AUACGAAU	202
MAP4K4--13-12565	12565	Chl	oooooooooooo o	m0m0000m0mmm0	UGUAGGAUGUCUA	203

TABLE 3-continued

Sense backbone, chemistry, and sequence information. o: phosphodiester; s: phosphorothioate; P: 5'phosphorylation; 0: 2'-OH; F: 2'-fluoro; m: 2'O-methyl; +: LNA modification. Capital letters in the sequence signify ribonucleotides, lower case letters signify deoxyribonucleotides.

ID Number	Oligo Number	OHang Sense Chem.	Sense Backbone	Sense Chemistry	Sense Sequence	SEQ ID NO:
MAP4K4-2931-16-12386.2	12386.2	chl	ooooooooooooo	0mm0m00000mmm0	CUGUGGAAGUCUA	204
MAP4K4-2931-13-12815	12815	chl	ooooooooooooo	m0m0m0m0m0m0m0m0m0m0m0m0	CUGUGGAAGUCUA	205
APOB--13-12957	12957	Chl TEG	oooooooooooss	0mmmmmmmmmmmmm	ACUGAAUACCAAU	206
MAP4K4--16-12983	12983	chl	oooooooooooss	mm0m00000mmm0	CUGUGGAAGUCUA	207
MAP4K4--16-12984	12984	Chl	oooooooooooooo	mm0m00000mmm0	CUGUGGAAGUCUA	208
MAP4K4--16-12985	12985	chl	oooooooooooss o	mmmmmmmmmmmmm	CUGUGGAAGUCUA	209
MAP4K4--16-12986	12986	chl	oooooooooooss o	mmmmmmmmmmmmm	CUGUGGAAGUCUA	210
MAP4K4--16-12987	12987	chl	oooooooooooss o	mm0m00000mmm0	CUGUGGAAGUCUA	211
MAP4K4--16-12988	12988	chl	oooooooooooss o	mm0m00000mmm0	CUGUGGAAGUCUA	212
MAP4K4--16-12989	12989	chl	oooooooooooss o	mm0m00000mmm0	CUGUGGAAGUCUA	213
MAP4K4--16-12990	12990	chl	oooooooooooss o	mm0m00000mmm0	CUGUGGAAGUCUA	214
MAP4K4--16-12991	12991	chl	oooooooooooss o	mm0m00000mmm0	CUGUGGAAGUCUA	215
MAP4K4--16-12992	12992	chl	oooooooooooss o	mm0m00000mmm0	CUGUGGAAGUCUA	216
MAP4K4--16-12993	12993	chl	oooooooooooss o	mm0m00000mmm0	CUGUGGAAGUCUA	217
MAP4K4--16-12994	12994	chl	oooooooooooss o	mm0m00000mmm0	CUGUGGAAGUCUA	218
MAP4K4--16-12995	12995	chl	oooooooooooss o	mm0m00000mmm0	CUGUGGAAGUCUA	219
MAP4K4-2931-19-13012	13012	chl	ooooooooooooooooooo	000000000000000000000	AGAGUUCUGUGGAAGUCUA	220
MAP4K4-2931-19-13016	13016	chl	ooooooooooooooooooo	DY547000000000000000000000	AGAGUUCUGUGGAAGUCUA	221
PPIB--13-13021	13021	Chl	ooooooooooooo	0mmm00mm0m000	AUUUGGCUACAAA	222
pGL3-1172-13-13038	13038	chl	ooooooooooooo	00m000m0m00mmm	ACAAAUACGAUUU	223
pGL3-1172-13-13040	13040	chl	ooooooooooooo	DY5470m000m0m00mmm	ACAAAUACGAUUU	224
--16-13047	13047	Chl	oooooooooooooo	mm0m00000mmm0	CUGUGGAAGUCUA	225

TABLE 3-continued

Sense backbone, chemistry, and sequence information. o: phosphodiester; s: phosphorothioate; P: 5'phosphorylation; 0: 2'-OH; F: 2'-fluoro; m: 2'O-methyl; +: LNA modification. Capital letters in the sequence signify ribonucleotides, lower case letters signify deoxyribonucleotides.

ID Number	Oligo Number	OHang Sense Chem.	Sense Backbone	Sense Chemistry	Sense Sequence	SEQ ID NO:
SOD1-530-13-13090	13090	chl	ooooooooooooo	00m00000000m0	AAUGAAGAAAGUA	226
SOD1-523-13-13091	13091	chl	ooooooooooooo	000m00000m000	AGGUGGAAAUGAA	227
SOD1-535-13-13092	13092	chl	ooooooooooooo	000000m0m0000	AGAAAGUACAAAG	228
SOD1-536-13-13093	13093	chl	ooooooooooooo	00000m0m00000	GAAAGUACAAAGA	229
SOD1-396-13-13094	13094	chl	ooooooooooooo	0m0m00mm0mm00	AUGUGACUGCUGA	230
SOD1-385-13-13095	13095	chl	ooooooooooooo	000mmm000m00m	AGACUUGGGCAAU	231
SOD1-195-13-13096	13096	chl	ooooooooooooo	0mmmm000m0000	AUUUCGAGCAGAA	232
APOB-4314-13-13115	13115	Chl	ooooooooooooo	0mmm0000000m0	AUCUGGAGAAACA	233
APOB-3384-13-13116	13116	Chl	ooooooooooooo	mm0000m000000	UCAGAACAAGAAA	234
APOB-3547-13-13117	13117	Chl	ooooooooooooo	00mmm0mmm0mm0	GACUCAUCUGCUA	235
APOB-4318-13-13118	13118	Chl	ooooooooooooo	0000000m00m0m	GGAGAAACAACAU	236
APOB-3741-13-13119	13119	Chl	ooooooooooooo	00mmmmm000m0	AGUCCCUCAAACA	237
PPIB--16-13136	13136	Chl	oooooooooooooo	00mm0m00000m0	GGCUACAAAAACA	238
APOB-4314-15-13154	13154	chl	oooooooooooooo	000mmm0000000m0	AGAUCUGGAGAAACA	239
APOB-3547-15-13155	13155	chl	oooooooooooooo	m000mmm0mmm0mm0	UGGACUCAUCUGCUA	240
APOB-4318-15-13157	13157	chl	oooooooooooooo	mm0000000m00m0m	CUGGAGAAACAACAU	241
APOB-3741-15-13158	13158	chl	oooooooooooooo	0000mmmmm000m0	AGAGUCCCUCAAACA	242
APOB--13-13159	13159	chl	oooooooooooo	0mm000m0mm00m	ACUGAAUACCAAU	243
APOB--15-13160	13160	chl	oooooooooooooo	0m0mm000m0mm00m	ACACUGAAUACCAAU	244
SOD1-530-16-13163	13163	chl	ooooooooooooo	00m00000000m0	AAUGAAGAAAGUA	245
SOD1-523-16-13164	13164	chl	ooooooooooooo	000m00000m000	AGGUGGAAAUGAA	246
SOD1-535-16-13165	13165	chl	ooooooooooooo	000000m0m0000	AGAAAGUACAAAG	247
SOD1-536-16-13166	13166	chl	ooooooooooooo	00000m0m00000	GAAAGUACAAAGA	248
SOD1-396-16-13167	13167	chl	ooooooooooooo	0m0m00mm0mm00	AUGUGACUGCUGA	249

TABLE 3-continued

Sense backbone, chemistry, and sequence information. o: phosphodiester; s: phosphorothioate; P: 5'phosphorylation; 0: 2'-OH; F: 2'-fluoro; m: 2'O-methyl; +: LNA modification. Capital letters in the sequence signify ribonucleotides, lower case letters signify deoxyribonucleotides.

ID Number	Oligo Number	OHang Sense Chem.	Sense Backbone	Sense Chemistry	Sense Sequence	SEQ ID NO:
SOD1-385-16-13168	13168	chl	oooooooooooo o	000mmm000m00m	AGACUUGGGCAAU	250
SOD1-195-16-13169	13169	chl	oooooooooooo o	0mmmm000m0000	AUUUCGAGCAGAA	251
pGL3-1172-16-13170	13170	chl	oooooooooooo o	0m000m0m00mmm	ACAAAUACGAUUU	252
pGL3-1172-16-13171	13171	chl	oooooooooooo o	DY5470m000m0m 00mmm	ACAAAUACGAUUU	253
MAP4k4-2931-19-13189	13189	chl	oooooooooooo ooooooo	0000000000000 00000000	AGAGUUCUGUGGA AGUCUA	254
CTGF-1222-13-13190	13190	Chl	oooooooooooo o	0m0000000m0m0	ACAGGAAGAUGUA	255
CTGF-813-13-13192	13192	Chl	oooooooooooo o	000m0000m0mmm	GAGUGGAGCGCCU	256
CTGF-747-13-13194	13194	Chl	oooooooooooo o	m00mm000000m0	CGACUGGAAGACA	257
CTGF-817-13-13196	13196	Chl	oooooooooooo o	0000m0mmm0mmm	GGAGCGCCUGUUC	258
CTGF-1174-13-13198	13198	Chl	oooooooooooo o	0mm0mm0m00mm0	GCCAUUACAACUG	259
CTGF-1005-13-13200	13200	Chl	oooooooooooo o	000mmmmm00mm	GAGCUUUCUGGCU	260
CTGF-814-13-13202	13202	Chl	oooooooooooo o	00m0000m0mmm0	AGUGGAGCGCCUG	261
CTGF-816-13-13204	13204	Chl	oooooooooooo o	m0000m0mmm0mm	UGGAGCGCCUGUU	262
CTGF-1001-13-13206	13206	Chl	oooooooooooo o	0mmm000mmmmmm	GUUUGAGCUUUCU	263
CTGF-1173-13-13208	13208	Chl	oooooooooooo o	m0mm0mm0m00mm	UGCCAUUACAACU	264
CTGF-749-13-13210	13210	Chl	oooooooooooo o	0mm000000m0m0	ACUGGAAGACACG	265
CTGF-792-13-13212	13212	Chl	oooooooooooo o	00mm0mmm00mmm	AACUGCCUGGUCC	266
CTGF-1162-13-13214	13214	Chl	oooooooooooo o	000mmm0m0mmm0	AGACCUGUGCCUG	267
CTGF-811-13-13216	13216	Chl	oooooooooooo o	m0000m0000m0m	CAGAGUGGAGCGC	268
CTGF-797-13-13218	13218	Chl	oooooooooooo o	mmm00mmm000mm	CCUGGUCCAGACC	269
CTGF-1175-13-13220	13220	Chl	oooooooooooo o	mm0mm0m00mm0m	CCAUUACAACUGU	270
CTGF-1172-13-13222	13222	Chl	oooooooooooo o	mm0mm0mm0m00m	CUGCCAUUACAAC	271
CTGF-1177-13-13224	13224	Chl	oooooooooooo o	0mm0m00mm0mmm	AUUACAACUGUCC	272

TABLE 3-continued

Sense backbone, chemistry, and sequence information. o: phosphodiester; s: phosphorothioate; P: 5'phosphorylation; 0: 2'-OH; F: 2'-fluoro; m: 2'O-methyl; +: LNA modification. Capital letters in the sequence signify ribonucleotides, lower case letters signify deoxyribonucleotides.

ID Number	Oligo Number	OHang Sense Chem.	Sense Backbone	Sense Chemistry	Sense Sequence	SEQ ID NO:
CTGF-1176-13-13226	13226	Chl	ooooooooooooo	m0mm0m00mm0mm	CAUUACAACUGUC	273
CTGF-812-13-13228	13228	Chl	ooooooooooooo	0000m0000m0mm	AGAGUGGAGCGCC	274
CTGF-745-13-13230	13230	Chl	ooooooooooooo	0mm00mm000000	ACCGACUGGAAGA	275
CTGF-1230-13-13232	13232	Chl	ooooooooooooo	0m0m0m00000m0	AUGUACGGAGACA	276
CTGF-920-13-13234	13234	Chl	ooooooooooooo	0mmmm0m0000mm	GCCUUGCGAAGCU	277
CTGF-679-13-13236	13236	Chl	ooooooooooooo	0mm0m000000m0	GCUGCGAGGAGUG	278
CTGF-992-13-13238	13238	Chl	ooooooooooooo	0mmm0mm000mmm	GCCUAUCAAGUUU	279
CTGF-1045-13-13240	13240	Chl	ooooooooooooo	00mmmm0m0000m	AAUUCUGUGGAGU	280
CTGF-1231-13-13242	13242	Chl	ooooooooooooo	m0m0m00000m0m	UGUACGGAGACAU	281
CTGF-991-13-13244	13244	Chl	ooooooooooooo	00mmm0mm000mm	AGCCUAUCAAGUU	282
CTGF-998-13-13246	13246	Chl	ooooooooooooo	m000mmm000mmm	CAAGUUUGAGCUU	283
CTGF-1049-13-13248	13248	Chl	ooooooooooooo	mm0m0000m0m0m	CUGUGGAGUAUGU	284
CTGF-1044-13-13250	13250	Chl	ooooooooooooo	000mmmm0m0000	AAAUUCUGUGGAG	285
CTGF-1327-13-13252	13252	Chl	ooooooooooooo	mmmm00m00m0m0	UUUCAGUAGCACA	286
CTGF-1196-13-13254	13254	Chl	ooooooooooooo	m00m00m0mmmmm	CAAUGACAUCUUU	287
CTGF-562-13-13256	13256	Chl	ooooooooooooo	00m0mm00m0m0m	AGUACCAGUGCAC	288
CTGF-752-13-13258	13258	Chl	ooooooooooooo	000000m0m0mmm	GGAAGACACGUUU	289
CTGF-994-13-13260	13260	Chl	ooooooooooooo	mm0mm000mmm00	CUAUCAAGUUUGA	290
CTGF-1040-13-13262	13262	Chl	ooooooooooooo	00mm000mmmm0m	AGCUAAAUUCUGU	291
CTGF-1984-13-13264	13264	Chl	ooooooooooooo	000m0000m0m00	AGGUAGAAUGUAA	292
CTGF-2195-13-13266	13266	Chl	ooooooooooooo	00mm00mm00mmm	AGCUGAUCAGUUU	293
CTGF-2043-13-13268	13268	Chl	ooooooooooooo	mmmm0mmm000m0	UUCUGCUCAGAUA	294
CTGF-1892-13-13270	13270	Chl	ooooooooooooo	mm0mmm000mm00	UUAUCUAAGUUAA	295
CTGF-1567-13-13272	13272	Chl	ooooooooooooo	m0m0m000m00m0	UAUACGAGUAAUA	296

TABLE 3-continued

Sense backbone, chemistry, and sequence information. o: phosphodiester; s: phosphorothioate; P: 5'phosphorylation; 0: 2'-OH; F: 2'-fluoro; m: 2'O-methyl; +: LNA modification. Capital letters in the sequence signify ribonucleotides, lower case letters signify deoxyribonucleotides.

ID Number	Oligo Number	OHang Sense Chem.	Sense Backbone	Sense Chemistry	Sense Sequence	SEQ ID NO:
CTGF-1780-13-13274	13274	Chl	oooooooooooo o	00mm000m00mmm	GACUGGACAGCUU	297
CTGF-2162-13-13276	13276	Chl	oooooooooooo o	0m00mmmmm0mm0	AUGGCCUUUAUUA	298
CTGF-1034-13-13278	13278	Chl	oooooooooooo o	0m0mm000mm000	AUACCGAGCUAAA	299
CTGF-2264-13-13280	13280	Chl	oooooooooooo o	mm0mm00000m0m	UUGUUGAGAGUGU	300
CTGF-1032-13-13282	13282	Chl	oooooooooooo o	0m0m0mm000mm0	ACAUACCGAGCUA	301
CTGF-1535-13-13284	13284	Chl	oooooooooooo o	00m0000000mm0	AGCAGAAAGGUUA	302
CTGF-1694-13-13286	13286	Chl	oooooooooooo o	00mm0mmmmm00	AGUUGUUCCUUAA	303
CTGF-1588-13-13288	13288	Chl	oooooooooooo o	0mmm0000m0m00	AUUUGAAGUGUAA	304
CTGF-928-13-13290	13290	Chl	oooooooooooo o	000mm00mmm000	AAGCUGACCUGGA	305
CTGF-1133-13-13292	13292	Chl	oooooooooooo o	00mm0m0000000	GGUCAUGAAGAAG	306
CTGF-912-13-13294	13294	Chl	oooooooooooo o	0m00mm000mmmm	AUGGUCAGGCCUU	307
CTGF-753-13-13296	13296	Chl	oooooooooooo o	00000m0m0mmm0	GAAGACACGUUUG	308
CTGF-918-13-13298	13298	Chl	oooooooooooo o	000mmmm0m0000	AGGCCUUGCGAAG	309
CTGF-744-13-13300	13300	Chl	oooooooooooo o	m0mm0mm00000	UACCGACUGGAAG	310
CTGF-466-13-13302	13302	Chl	oooooooooooo o	0mm0m0000mm0	ACCGCAAGAUCGG	311
CTGF-917-13-13304	13304	Chl	oooooooooooo o	m000mmmm0m000	CAGGCCUUGCGAA	312
CTGF-1038-13-13306	13306	Chl	oooooooooooo o	m000mm000mmmm	CGAGCUAAAUUCU	313
CTGF-1048-13-13308	13308	Chl	oooooooooooo o	mmm0m0000m0m0	UCUGUGGAGUAUG	314
CTGF-1235-13-13310	13310	Chl	oooooooooooo o	m00000m0m00m0	CGGAGACAUGGCA	315
CTGF-868-13-13312	13312	Chl	oooooooooooo o	0m00m00m0mmmm	AUGACAACGCCUC	316
CTGF-1131-13-13314	13314	Chl	oooooooooooo o	0000mm0m00000	GAGGUCAUGAAGA	317
CTGF-1043-13-13316	13316	Chl	oooooooooooo o	m000mmmm0m000	UAAAUUCUGUGGA	318
CTGF-751-13-13318	13318	Chl	oooooooooooo o	m000000m0m0mm	UGGAAGACACGUU	319

TABLE 3-continued

Sense backbone, chemistry, and sequence information. o: phosphodiester; s: phosphorothioate; P: 5'phosphorylation; 0: 2'-OH; F: 2'-fluoro; m: 2'O-methyl; +: LNA modification. Capital letters in the sequence signify ribonucleotides, lower case letters signify deoxyribonucleotides.

ID Number	Oligo Number	OHang Sense Chem.	Sense Backbone	Sense Chemistry	Sense Sequence	SEQ ID NO:
CTGF-1227-13-13320	13320	Chl	oooooooooooo o	0000m0m0m0000	AAGAUGUACGGAG	320
CTGF-867-13-13322	13322	Chl	oooooooooooo o	00m00m00m0mmm	AAUGACAACGCCU	321
CTGF-1128-13-13324	13324	Chl	oooooooooooo o	00m0000mm0m00	GGCGAGGUCAUGA	322
CTGF-756-13-13326	13326	Chl	oooooooooooo o	00m0m0mmm00mm	GACACGUUUGGCC	323
CTGF-1234-13-13328	13328	Chl	oooooooooooo o	0m00000m0m00m	ACGGAGACAUGGC	324
CTGF-916-13-13330	13330	Chl	oooooooooooo o	mm000mmmm0m00	UCAGGCCUUGCGA	325
CTGF-925-13-13332	13332	Chl	oooooooooooo o	0m0000mm00mmm	GCGAAGCUGACCU	326
CTGF-1225-13-13334	13334	Chl	oooooooooooo o	000000m0m0m00	GGAAGAUGUACGG	327
CTGF-445-13-13336	13336	Chl	oooooooooooo o	0m00mmmm00mmm	GUGACUUCGGCUC	328
CTGF-446-13-13338	13338	Chl	oooooooooooo o	m00mmmm00mmmm	UGACUUCGGCUCC	329
CTGF-913-13-13340	13340	Chl	oooooooooooo o	m00mm000mmmm0	UGGUCAGGCCUUG	330
CTGF-997-13-13342	13342	Chl	oooooooooooo o	mm000mmm000mm	UCAAGUUUGAGCU	331
CTGF-277-13-13344	13344	Chl	oooooooooooo o	0mm0000mm0m00	GCCAGAACUGCAG	332
CTGF-1052-13-13346	13346	Chl	oooooooooooo o	m0000m0m0m0mm	UGGAGUAUGUACC	333
CTGF-887-13-13348	13348	Chl	oooooooooooo o	0mm0000000m00	GCUAGAGAAGCAG	334
CTGF-914-13-13350	13350	Chl	oooooooooooo o	00mm000mmmm0m	GGUCAGGCCUUGC	335
CTGF-1039-13-13352	13352	Chl	oooooooooooo o	000mm000mmmm0	GAGCUAAAUUCUG	336
CTGF-754-13-13354	13354	Chl	oooooooooooo o	0000m0m0mmm00	AAGACACGUUUGG	337
CTGF-1130-13-13356	13356	Chl	oooooooooooo o	m0000mm0m0000	CGAGGUCAUGAAG	338
CTGF-919-13-13358	13358	Chl	oooooooooooo o	00mmmm0m0000m	GGCCUUGCGAAGC	339
CTGF-922-13-13360	13360	Chl	oooooooooooo o	mmm0m0000mm00	CUUGCGAAGCUGA	340
CTGF-746-13-13362	13362	Chl	oooooooooooo o	mm00mm000000m	CCGACUGGAAGAC	341
CTGF-993-13-13364	13364	Chl	oooooooooooo o	mmm0mm000mmm0	CCUAUCAAGUUUG	342

TABLE 3-continued

Sense backbone, chemistry, and sequence information. o: phosphodiester; s: phosphorothioate; P: 5'phosphorylation; 0: 2'-OH; F: 2'-fluoro; m: 2'O-methyl; +: LNA modification. Capital letters in the sequence signify ribonucleotides, lower case letters signify deoxyribonucleotides.

ID Number	Oligo Number	OHang Sense Chem.	Sense Backbone	Sense Chemistry	Sense Sequence	SEQ ID NO:
CTGF-825-13-13366	13366	Chl	oooooooooooo o	m0mmmm0000mmm	UGUUCCAAGACCU	343
CTGF-926-13-13368	13368	Chl	oooooooooooo o	m0000mm00mmm0	CGAAGCUGACCUG	344
CTGF-923-13-13370	13370	Chl	oooooooooooo o	mm0m0000mm00m	UUGCGAAGCUGAC	345
CTGF-866-13-13372	13372	Chl	oooooooooooo o	m00m00m00m0mm	CAAUGACAACGCC	346
CTGF-563-13-13374	13374	Chl	oooooooooooo o	0m0mm00m0m0m0	GUACCAGUGCACG	347
CTGF-823-13-13376	13376	Chl	oooooooooooo o	mmm0mmmm0000m	CCUGUUCCAAGAC	348
CTGF-1233-13-13378	13378	Chl	oooooooooooo o	m0m00000m0m00	UACGGAGACAUGG	349
CTGF-924-13-13380	13380	Chl	oooooooooooo o	m0m0000mm00mm	UGCGAAGCUGACC	350
CTGF-921-13-13382	13382	Chl	oooooooooooo o	mmmm0m0000mm0	CCUUGCGAAGCUG	351
CTGF-443-13-13384	13384	Chl	oooooooooooo o	mm0m00mmmm00m	CUGUGACUUCGGC	352
CTGF-1041-13-13386	13386	Chl	oooooooooooo o	0mm000mmmm0m0	GCUAAAUUCUGUG	353
CTGF-1042-13-13388	13388	Chl	oooooooooooo o	mm000mmmm0m00	CUAAAUUCUGUGG	354
CTGF-755-13-13390	13390	Chl	oooooooooooo o	000m0m0mmm00m	AGACACGUUUGGC	355
CTGF-467-13-13392	13392	Chl	oooooooooooo o	mm0m0000mm00m	CCGCAAGAUCGGC	356
CTGF-995-13-13394	13394	Chl	oooooooooooo o	m0mm000mmm000	UAUCAAGUUUGAG	357
CTGF-927-13-13396	13396	Chl	oooooooooooo o	0000mm00mmm00	GAAGCUGACCUGG	358
SPP1-1025-13-13398	13398	Chl	oooooooooooo o	mmm0m000mm000	CUCAUGAAUUAGA	359
SPP1-1049-13-13400	13400	Chl	oooooooooooo o	mm0000mm00mm0	CUGAGGUCAAUUA	360
SPP1-1051-13-13402	13402	Chl	oooooooooooo o	0000mm00mm000	GAGGUCAAUUAAA	361
SPP1-1048-13-13404	13404	Chl	oooooooooooo o	mmm0000mm00mm	UCUGAGGUCAAUU	362
SPP1-1050-13-13406	13406	Chl	oooooooooooo o	m0000mm00mm00	UGAGGUCAAUUAA	363
SPP1-1047-13-13408	13408	Chl	oooooooooooo o	mmmm0000mm00m	UUCUGAGGUCAAU	364
SPP1-800-13-13410	13410	Chl	oooooooooooo o	0mm00mm000m00	GUCAGCUGGAUGA	365

TABLE 3-continued

Sense backbone, chemistry, and sequence information. o: phosphodiester; s: phosphorothioate; P: 5'phosphorylation; 0: 2'-OH; F: 2'-fluoro; m: 2'O-methyl; +: LNA modification. Capital letters in the sequence signify ribonucleotides, lower case letters signify deoxyribonucleotides.

ID Number	Oligo Number	OHang Sense Chem.	Sense Backbone	Sense Chemistry	Sense Sequence	SEQ ID NO:
SPP1-492-13-13412	13412	Chl	ooooooooooooo	mmmm00m000mmm	UUCUGAUGAAUCU	366
SPP1-612-13-13414	13414	Chl	ooooooooooooo	m000mm0000mm0	UGGACUGAGGUCA	367
SPP1-481-13-13416	13416	Chl	ooooooooooooo	000mmmm0mm0mm	GAGUCUCACCAUU	368
SPP1-614-13-13418	13418	Chl	ooooooooooooo	00mm0000mm000	GACUGAGGUCAAA	369
SPP1-951-13-13420	13420	Chl	ooooooooooooo	mm0m00mm0m000	UCACAGCCAUGAA	370
SPP1-482-13-13422	13422	Chl	ooooooooooooo	00mmmm0mm0mmm	AGUCUCACCAUUC	371
SPP1-856-13-13424	13424	Chl	ooooooooooooo	000m000000mm0	AAGCGGAAAGCCA	372
SPP1-857-13-13426	13426	Chl	ooooooooooooo	00m000000mm00	AGCGGAAAGCCAA	373
SPP1-365-13-13428	13428	Chl	ooooooooooooo	0mm0m0m000m00	ACCACAUGGAUGA	374
SPP1-359-13-13430	13430	Chl	ooooooooooooo	0mm0m00mm0m0m	GCCAUGACCACAU	375
SPP1-357-13-13432	13432	Chl	ooooooooooooo	000mm0m00mm0m	AAGCCAUGACCAC	376
SPP1-858-13-13434	13434	Chl	ooooooooooooo	0m000000mm00m	GCGGAAAGCCAAU	377
SPP1-1012-13-13436	13436	Chl	ooooooooooooo	000mmmm0m0mmm	AAAUUUCGUAUUU	378
SPP1-1014-13-13438	13438	Chl	ooooooooooooo	0mmmm0m0mmmmm	AUUUCGUAUUUCU	379
SPP1-356-13-13440	13440	Chl	ooooooooooooo	0000mm0m00mm0	AAAGCCAUGACCA	380
SPP1-368-13-13442	13442	Chl	ooooooooooooo	0m0m000m00m0m	ACAUGGAUGAUAU	381
SPP1-1011-13-13444	13444	Chl	ooooooooooooo	0000mmmm0m0mm	GAAAUUUCGUAUU	382
SPP1-754-13-13446	13446	Chl	ooooooooooooo	0m0mmmmmm00mm	GCGCCUUCUGAUU	383
SPP1-1021-13-13448	13448	Chl	ooooooooooooo	0mmmmmm0m000m	AUUUCUCAUGAAU	384
SPP1-1330-13-13450	13450	Chl	ooooooooooooo	mmmmm0m000m00	CUCUCAUGAAUAG	385
SPP1-346-13-13452	13452	Chl	ooooooooooooo	000mmm00m0000	AAGUCCAACGAAA	386
SPP1-869-13-13454	13454	Chl	ooooooooooooo	0m00m00000m00	AUGAUGAGAGCAA	387
SPP1-701-13-13456	13456	Chl	ooooooooooooo	0m000000mm000	GCGAGGAGUUGAA	388

TABLE 3-continued

Sense backbone, chemistry, and sequence information. o: phosphodiester; s: phosphorothioate; P: 5'phosphorylation; 0: 2'-OH; F: 2'-fluoro; m: 2'O-methyl; +: LNA modification. Capital letters in the sequence signify ribonucleotides, lower case letters signify deoxyribonucleotides.

ID Number	Oligo Number	OHang Sense Chem.	Sense Backbone	Sense Chemistry	Sense Sequence	SEQ ID NO:
SPP1-896-13-13458	13458	Chl	oooooooooooo o	m00mm00m00mm0	UGAUUGAUAGUCA	389
SPP1-1035-13-13460	13460	Chl	oooooooooooo o	000m00m0m0mmm	AGAUAGUGCAUCU	390
SPP1-1170-13-13462	13462	Chl	oooooooooooo o	0m0m0m0mmm0mm	AUGUGUAUCUAUU	391
SPP1-1282-13-13464	13464	Chl	oooooooooooo o	mmmm0m0000000	UUCUAUAGAAGAA	392
SPP1-1537-13-13466	13466	Chl	oooooooooooo o	mm0mmm00m00mm	UUGUCCAGCAAUU	393
SPP1-692-13-13468	13468	Chl	oooooooooooo o	0m0m000000m00	ACAUGGAAAGCGA	394
SPP1-840-13-13470	13470	Chl	oooooooooooo o	0m00mmm000mm0	GCAGUCCAGAUUA	395
SPP1-1163-13-13472	13472	Chl	oooooooooooo o	m00mm000m0m0m	UGGUUGAAUGUGU	396
SPP1-789-13-13474	13474	Chl	oooooooooooo o	mm0m0000m000m	UUAUGAAACGAGU	397
SPP1-841-13-13476	13476	Chl	oooooooooooo o	m00mmm000mm0m	CAGUCCAGAUUAU	398
SPP1-852-13-13478	13478	Chl	oooooooooooo o	0m0m000m00000	AUAUAAGCGGAAA	399
SPP1-209-13-13480	13480	Chl	oooooooooooo o	m0mm00mm000m0	UACCAGUUAAACA	400
SPP1-1276-13-13482	13482	Chl	oooooooooooo o	m0mmm0mmmm0m0	UGUUCAUUCUAUA	401
SPP1-137-13-13484	13484	Chl	oooooooooooo o	mm00mm0000000	CCGACCAAGGAAA	402
SPP1-711-13-13486	13486	Chl	oooooooooooo o	000m00m0m0m0m	GAAUGGUGCAUAC	403
SPP1-582-13-13488	13488	Chl	oooooooooooo o	0m0m00m00mm00	AUAUGAUGGCCGA	404
SPP1-839-13-13490	13490	Chl	oooooooooooo o	00m00mmm000mm	AGCAGUCCAGAUU	405
SPP1-1091-13-13492	13492	Chl	oooooooooooo o	0m0mmm00mm000	GCAUUUAGUCAAA	406
SPP1-884-13-13494	13494	Chl	oooooooooooo o	00m0mmmm00m0m	AGCAUUCCGAUGU	407
SPP1-903-13-13496	13496	Chl	oooooooooooo o	m00mm00000mmm	UAGUCAGGAACUU	408
SPP1-1090-13-13498	13498	Chl	oooooooooooo o	m0m0mmm00mm00	UGCAUUUAGUCAA	409
SPP1-474-13-13500	13500	Chl	oooooooooooo o	0mmm00m000mmm	GUCUGAUGAGUCU	410
SPP1-575-13-13502	13502	Chl	oooooooooooo o	m000m0m0m0m00	UAGACACAUAUGA	411

TABLE 3-continued

Sense backbone, chemistry, and sequence information. o: phosphodiester; s: phosphorothioate; P: 5'phosphorylation; 0: 2'-OH; F: 2'-fluoro; m: 2'O-methyl; +: LNA modification. Capital letters in the sequence signify ribonucleotides, lower case letters signify deoxyribonucleotides.

ID Number	Oligo Number	OHang Sense Chem.	Sense Backbone	Sense Chemistry	Sense Sequence	SEQ ID NO:
SPP1-671-13-13504	13504	Chl	ooooooooooooo	m000m00000m0m	CAGACGAGGACAU	412
SPP1-924-13-13506	13506	Chl	ooooooooooooo	m00mm0m000mmm	CAGCCGUGAAUUC	413
SPP1-1185-13-13508	13508	Chl	ooooooooooooo	00mmm00000m00	AGUCUGGAAAUAA	414
SPP1-1221-13-13510	13510	Chl	ooooooooooooo	00mmm0m00mmmm	AGUUUGUGGCUUC	415
SPP1-347-13-13512	13512	Chl	ooooooooooooo	00mmm00m00000	AGUCCAACGAAAG	416
SPP1-634-13-13514	13514	Chl	ooooooooooooo	000mmmm0m000m	AAGUUUCGCAGAC	417
SPP1-877-13-13516	13516	Chl	ooooooooooooo	00m00m000m0mm	AGCAAUGAGCAUU	418
SPP1-1033-13-13518	13518	Chl	ooooooooooooo	mm000m00m0m0m	UUAGAUAGUGCAU	419
SPP1-714-13-13520	13520	Chl	ooooooooooooo	m00m0m0m0m000	UGGUGCAUACAAG	420
SPP1-791-13-13522	13522	Chl	ooooooooooooo	0m0000m000mm0	AUGAAACGAGUCA	421
SPP1-813-13-13524	13524	Chl	ooooooooooooo	mm0000m0mm000	CCAGAGUGCUGAA	422
SPP1-939-13-13526	13526	Chl	ooooooooooooo	m00mm0m000mmm	CAGCCAUGAAUUU	423
SPP1-1161-13-13528	13528	Chl	ooooooooooooo	0mm00mm000m0m	AUUGGUUGAAUGU	424
SPP1-1164-13-13530	13530	Chl	ooooooooooooo	00mm000m0m0m0	GGUUGAAUGUGUA	425
SPP1-1190-13-13532	13532	Chl	ooooooooooooo	00000m00mm00m	GGAAAUAACUAAU	426
SPP1-1333-13-13534	13534	Chl	ooooooooooooo	mm0m000m00000	UCAUGAAUAGAAA	427
SPP1-537-13-13536	13536	Chl	ooooooooooooo	0mm00m00mm000	GCCAGCAACCGAA	428
SPP1-684-13-13538	13538	Chl	ooooooooooooo	m0mmmm0m0m0m0	CACCUCACACAUG	429
SPP1-707-13-13540	13540	Chl	ooooooooooooo	00mm000m00m0m	AGUUGAAUGGUGC	430
SPP1-799-13-13542	13542	Chl	ooooooooooooo	00mm00mm000m0	AGUCAGCUGGAUG	431
SPP1-853-13-13544	13544	Chl	ooooooooooooo	m0m000m000000	UAUAAGCGGAAAG	432
SPP1-888-13-13546	13546	Chl	ooooooooooooo	mmmm00m0m00mm	UUCCGAUGUGAUU	433
SPP1-1194-13-13548	13548	Chl	ooooooooooooo	0m00mm00m0m0m	AUAACUAAUGUGU	434

TABLE 3-continued

Sense backbone, chemistry, and sequence information. o: phosphodiester; s: phosphorothioate; P: 5'phosphorylation; 0: 2'-OH; F: 2'-fluoro; m: 2'O-methyl; +: LNA modification. Capital letters in the sequence signify ribonucleotides, lower case letters signify deoxyribonucleotides.

ID Number	Oligo Number	OHang Sense Chem.	Sense Backbone	Sense Chemistry	Sense Sequence	SEQ ID NO:
SPP1-1279-13-13550	13550	Chl	ooooooooooooo	mm0mmmm0m0000	UCAUUCUAUAGAA	435
SPP1-1300-13-13552	13552	Chl	ooooooooooooo	00mm0mm0mm0m0	AACUAUCACUGUA	436
SPP1-1510-13-13554	13554	Chl	ooooooooooooo	0mm00mm0mmm0m	GUCAAUUGCUUAU	437
SPP1-1543-13-13556	13556	Chl	ooooooooooooo	00m00mm00m000	AGCAAUUAAUAAA	438
SPP1-434-13-13558	13558	Chl	ooooooooooooo	0m00mmmm00m00	ACGACUCUGAUGA	439
SPP1-600-13-13560	13560	Chl	ooooooooooooo	m00m0m00mmm0m	UAGUGUGGUUUAU	440
SPP1-863-13-13562	13562	Chl	ooooooooooooo	000mm00m00m00	AAGCCAAUGAUGA	441
SPP1-902-13-13564	13564	Chl	ooooooooooooo	0m00mm00000mm	AUAGUCAGGAACU	442
SPP1-921-13-13566	13566	Chl	ooooooooooooo	00mm00mm0m000	AGUCAGCCGUGAA	443
SPP1-154-13-13568	13568	Chl	ooooooooooooo	0mm0mm0m00000	ACUACCAUGAGAA	444
SPP1-217-13-13570	13570	Chl	ooooooooooooo	000m000mm00mm	AAACAGGCUGAUU	445
SPP1-816-13-13572	13572	Chl	ooooooooooooo	000mmm0000mm	GAGUGCUGAAACC	446
SPP1-882-13-13574	13574	Chl	ooooooooooooo	m000m0mmmm00m	UGAGCAUUCCGAU	447
SPP1-932-13-13576	13576	Chl	ooooooooooooo	00mmmm0m00mm0	AAUUCCACAGCCA	448
SPP1-1509-13-13578	13578	Chl	ooooooooooooo	m0mm00mm0mmm0	UGUCAAUUGCUUA	449
SPP1-157-13-13580	13580	Chl	ooooooooooooo	0mm0m00000mm0	ACCAUGAGAAUUG	450
SPP1-350-13-13582	13582	Chl	ooooooooooooo	mm00m00000mm0	CCAACGAAAGCCA	451
SPP1-511-13-13584	13584	Chl	ooooooooooooo	mm00mm0mm00mm	CUGGUCACUGAUU	452
SPP1-605-13-13586	13586	Chl	ooooooooooooo	m00mmm0m000mm	UGGUUUAUGGACU	453
SPP1-811-13-13588	13588	Chl	ooooooooooooo	00mm0000m0mm0	GACCAGAGUGCUG	454
SPP1-892-13-13590	13590	Chl	ooooooooooooo	00m0m00mm00m0	GAUGUGAUUGAUA	455
SPP1-922-13-13592	13592	Chl	ooooooooooooo	0mm00mm0m000m	GUCAGCCGUGAAU	456
SPP1-1169-13-13594	13594	Chl	ooooooooooooo	00m0m0m0mmm0m	AAUGUGUAUCUAU	457

TABLE 3-continued

Sense backbone, chemistry, and sequence information. o: phosphodiester; s: phosphorothioate; P: 5'phosphorylation; 0: 2'-OH; F: 2'-fluoro; m: 2'O-methyl; +: LNA modification. Capital letters in the sequence signify ribonucleotides, lower case letters signify deoxyribonucleotides.

ID Number	Oligo Number	OHang Sense Chem.	Sense Backbone	Sense Chemistry	Sense Sequence	SEQ ID NO:
SPP1-1182-13-13596	13596	Chl	ooooooooooooo	mm000mmm00000	UUGAGUCUGGAAA	458
SPP1-1539-13-13598	13598	Chl	ooooooooooooo	0mmm00m00mm00	GUCCAGCAAUUAA	459
SPP1-1541-13-13600	13600	Chl	ooooooooooooo	mm00m00mm00m0	CCAGCAAUUAAUA	460
SPP1-427-13-13602	13602	Chl	ooooooooooooo	00mmm000m00mm	GACUCGAACGACU	461
SPP1-533-13-13604	13604	Chl	ooooooooooooo	0mmm0mm00m00m	ACCUGCCAGCAAC	462
APOB--13-13763	13763	Chl TEG	ooooooooooooo	0m+00+m0+m0+m	ACtGAaUAcCAaU	463
APOB--13-13764	13764	Chl TEG	ooooooooooooo	0mm000m0mm00m	ACUGAAUACCAAU	464
MAP4K4--16-13766	13766	Chl	ooooooooooooo	DY547mm0m00000mmm0	CUGUGGAAGUCUA	465
PPIB--13-13767	13767	Chl	ooooooooooooo	mmmmmmmmmmmmm	GGCUACAAAAACA	466
PPIB--15-13768	13768	Chl	ooooooooooooooo	mm00mm0m00000m0	UUGGCUACAAAAACA	467
PPIB--17-13769	13769	Chl	ooooooooooooooooo	0mmm00mm0m00000m0	AUUUGGCUACAAAAACA	468
MAP4K4--16-13939	13939	Chl	ooooooooooooo	m0m0000m0mmm0	UGUAGGAUGUCUA	469
APOB-4314-16-13940	13940	Chl	ooooooooooooo	0mmm0000000m0	AUCUGGAGAAACA	470
APOB-4314-17-13941	13941	Chl	ooooooooooooooo	000mmm0000000m0	AGAUCUGGAGAAACA	471
APOB--16-13942	13942	Chl	ooooooooooooo	00mmm0mmm0mm0	GACUCAUCUGCUA	472
APOB--18-13943	13943	Chl	ooooooooooooo	00mmm0mmm0mm0	GACUCAUCUGCUA	473
APOB--17-13944	13944	Chl	ooooooooooooooo	m000mmm0mmm0mm0	UGGACUCAUCUGCUA	474
APOB--19-13945	13945	Chl	ooooooooooooooo	m000mmm0mmm0mm0	UGGACUCAUCUGCUA	475
APOB-4314-16-13946	13946	Chl	ooooooooooooo	0000000m00m0m	GGAGAAACAACAU	476
APOB-4314-17-13947	13947	Chl	ooooooooooooooo	mm0000000m00m0m	CUGGAGAAACAACAU	477
APOB--16-13948	13948	Chl	ooooooooooooo	00mmmmm000m0	AGUCCCUCAAACA	478
APOB--17-13949	13949	Chl	ooooooooooooooo	0000mmmmm000m0	AGAGUCCCUCAAACA	479
APOB--16-13950	13950	Chl	ooooooooooooo	0mm000m0mm00m	ACUGAAUACCAAU	480
APOB--18-13951	13951	Chl	ooooooooooooo	0mm000m0mm00m	ACUGAAUACCAAU	481

TABLE 3-continued

Sense backbone, chemistry, and sequence information. o: phosphodiester; s: phosphorothioate; P: 5'phosphorylation; 0: 2'-OH; F: 2'-fluoro; m: 2'O-methyl; +: LNA modification. Capital letters in the sequence signify ribonucleotides, lower case letters signify deoxyribonucleotides.

ID Number	Oligo Number	OHang Sense Chem.	Sense Backbone	Sense Chemistry	Sense Sequence	SEQ ID NO:
APOB--17-13952	13952	Chl	ooooooooooooooo	0m0mm000m0mm00m	ACACUGAAUACCAAU	482
APOB--19-13953	13953	Chl	ooooooooooooooo	0m0mm000m0mm00m	ACACUGAAUACCAAU	483
MAP4K4--16-13766.2	13766.2	Chl	ooooooooooooo	DY547mm0m00000mmm0	CUGUGGAAGUCUA	484
CTGF-1222-16-13980	13980	Chl	ooooooooooooo	0m0000000m0m0	ACAGGAAGAUGUA	485
CTGF-813-16-13981	13981	Chl	ooooooooooooo	000m0000mmmm	GAGUGGAGCGCCU	486
CTGF-747-16-13982	13982	Chl	ooooooooooooo	m0mm000000m0	CGACUGGAAGACA	487
CTGF-817-16-13983	13983	Chl	ooooooooooooo	0000mmmm0mmm	GGAGCGCCUGUUC	488
CTGF-1174-16-13984	13984	Chl	ooooooooooooo	0mm0mm0m00mm0	GCCAUUACAACUG	489
CTGF-1005-16-13985	13985	Chl	ooooooooooooo	000mmmmmm00mm	GAGCUUUCUGGCU	490
CTGF-814-16-13986	13986	Chl	ooooooooooooo	00m0000mmmm0	AGUGGAGCGCCUG	491
CTGF-816-16-13987	13987	Chl	ooooooooooooo	m0000mmmm0mm	UGGAGCGCCUGUU	492
CTGF-1001-16-13988	13988	Chl	ooooooooooooo	0mmm000mmmmmm	GUUUGAGCUUUCU	493
CTGF-1173-16-13989	13989	Chl	ooooooooooooo	m0mm0mm0m00mm	UGCCAUUACAACU	494
CTGF-749-16-13990	13990	Chl	ooooooooooooo	0mm000000m0m	ACUGGAAGACACG	495
CTGF-792-16-13991	13991	Chl	ooooooooooooo	00mm0mmm00mmm	AACUGCCUGGUCC	496
CTGF-1162-16-13992	13992	Chl	ooooooooooooo	000mmm0m0mmm0	AGACCUGUGCCUG	497
CTGF-811-16-13993	13993	Chl	ooooooooooooo	m0000m0000mm	CAGAGUGGAGCGC	498
CTGF-797-16-13994	13994	Chl	ooooooooooooo	mmm00mmm000mm	CCUGGUCCAGACC	499
CTGF-1175-16-13995	13995	Chl	ooooooooooooo	mm0mm0m00mm0m	CCAUUACAACUGU	500
CTGF-1172-16-13996	13996	Chl	ooooooooooooo	mm0mm0mm0m00m	CUGCCAUUACAAC	501
CTGF-1177-16-13997	13997	Chl	ooooooooooooo	0mm0m00mm0mmm	AUUACAACUGUCC	502
CTGF-1176-16-13998	13998	Chl	ooooooooooooo	m0mm0m00mm0mm	CAUUACAACUGUC	503
CTGF-812-16-13999	13999	Chl	ooooooooooooo	0000m0000mmm	AGAGUGGAGCGCC	504
CTGF-745-16-14000	14000	Chl	ooooooooooooo	0mm0mm000000	ACCGACUGGAAGA	505

TABLE 3-continued

Sense backbone, chemistry, and sequence information. o: phosphodiester; s: phosphorothioate; P: 5'phosphorylation; 0: 2'-OH; F: 2'-fluoro; m: 2'O-methyl; +: LNA modification. Capital letters in the sequence signify ribonucleotides, lower case letters signify deoxyribonucleotides.

ID Number	Oligo Number	OHang Sense Chem.	Sense Backbone	Sense Chemistry	Sense Sequence	SEQ ID NO:
CTGF-1230-16-14001	14001	Chl	ooooooooooooo	0m0m0m0000m0	AUGUACGGAGACA	506
CTGF-920-16-14002	14002	Chl	ooooooooooooo	0mmmm0m000mm	GCCUUGCGAAGCU	507
CTGF-679-16-14003	14003	Chl	ooooooooooooo	0mm0m00000m0	GCUGCGAGGAGUG	508
CTGF-992-16-14004	14004	Chl	ooooooooooooo	0mmm0mm000mmm	GCCUAUCAAGUUU	509
CTGF-1045-16-14005	14005	Chl	ooooooooooooo	00mmmm0m0000m	AAUUCUGUGGAGU	510
CTGF-1231-16-14006	14006	Chl	ooooooooooooo	m0m0m0000m0m	UGUACGGAGACAU	511
CTGF-991-16-14007	14007	Chl	ooooooooooooo	00mmm0mm000mm	AGCCUAUCAAGUU	512
CTGF-998-16-14008	14008	Chl	ooooooooooooo	m000mmm000mmm	CAAGUUUGAGCUU	513
CTGF-1049-16-14009	14009	Chl	ooooooooooooo	mm0m0000m0m0m	CUGUGGAGUAUGU	514
CTGF-1044-16-14010	14010	Chl	ooooooooooooo	000mmmm0m0000	AAAUUCUGUGGAG	515
CTGF-1327-16-14011	14011	Chl	ooooooooooooo	mmmm00m00m0m0	UUUCAGUAGCACA	516
CTGF-1196-16-14012	14012	Chl	ooooooooooooo	m00m00m0mmmmm	CAAUGACAUCUUU	517
CTGF-562-16-14013	14013	Chl	ooooooooooooo	00m0mm00m0m0m	AGUACCAGUGCAC	518
CTGF-752-16-14014	14014	Chl	ooooooooooooo	000000m0mmmm	GGAAGACACGUUU	519
CTGF-994-16-14015	14015	Chl	ooooooooooooo	mm0mm000mmm00	CUAUCAAGUUUGA	520
CTGF-1040-16-14016	14016	Chl	ooooooooooooo	00mm000mmmm0m	AGCUAAAUUCUGU	521
CTGF-1984-16-14017	14017	Chl	ooooooooooooo	000m0000m0m00	AGGUAGAAUGUAA	522
CTGF-2195-16-14018	14018	Chl	ooooooooooooo	00mm00mm00mmm	AGCUGAUCAGUUU	523
CTGF-2043-16-14019	14019	Chl	ooooooooooooo	mmmm0mmm000m0	UUCUGCUCAGAUA	524
CTGF-1892-16-14020	14020	Chl	ooooooooooooo	mm0mmm000mm00	UUAUCUAAGUUAA	525
CTGF-1567-16-14021	14021	Chl	ooooooooooooo	m0m0m00m00m0	UAUACGAGUAAUA	526
CTGF-1780-16-14022	14022	Chl	ooooooooooooo	00mm000m00mmm	GACUGGACAGCUU	527
CTGF-2162-16-14023	14023	Chl	ooooooooooooo	0m00mmmmm0mm0	AUGGCCUUUAUUA	528
CTGF-1034-16-14024	14024	Chl	ooooooooooooo	0m0mm00mm000	AUACCGAGCUAAA	529

TABLE 3-continued

Sense backbone, chemistry, and sequence information. o: phosphodiester; s: phosphorothioate; P: 5'phosphorylation; 0: 2'-OH; F: 2'-fluoro; m: 2'O-methyl; +: LNA modification. Capital letters in the sequence signify ribonucleotides, lower case letters signify deoxyribonucleotides.

ID Number	Oligo Number	OHang Sense Chem.	Sense Backbone	Sense Chemistry	Sense Sequence	SEQ ID NO:
CTGF-2264-16-14025	14025	Chl	oooooooooooo o	mm0mm00000m0m	UUGUUGAGAGUGU	530
CTGF-1032-16-14026	14026	Chl	oooooooooooo o	0m0m0mm00mm0	ACAUACCGAGCUA	531
CTGF-1535-16-14027	14027	Chl	oooooooooooo o	00m0000000mm0	AGCAGAAAGGUUA	532
CTGF-1694-16-14028	14028	Chl	oooooooooooo o	00mm0mmmmm00	AGUUGUUCCUUAA	533
CTGF-1588-16-14029	14029	Chl	oooooooooooo o	0mmm0000m0m00	AUUUGAAGUGUAA	534
CTGF-928-16-14030	14030	Chl	oooooooooooo o	000mm00mmm000	AAGCUGACCUGGA	535
CTGF-1133-16-14031	14031	Chl	oooooooooooo o	00mm0m0000000	GGUCAUGAAGAAG	536
CTGF-912-16-14032	14032	Chl	oooooooooooo o	0m00mm000mmmm	AUGGUCAGGCCUU	537
CTGF-753-16-14033	14033	Chl	oooooooooooo o	00000m0mmmm0	GAAGACACGUUUG	538
CTGF-918-16-14034	14034	Chl	oooooooooooo o	000mmmm0m000	AGGCCUUGCGAAG	539
CTGF-744-16-14035	14035	Chl	oooooooooooo o	m0mm0mm00000	UACCGACUGGAAG	540
CTGF-466-16-14036	14036	Chl	oooooooooooo o	0mmm0000mm0	ACCGCAAGAUCGG	541
CTGF-917-16-14037	14037	Chl	oooooooooooo o	m000mmmm0m00	CAGGCCUUGCGAA	542
CTGF-1038-16-14038	14038	Chl	oooooooooooo o	m00mm000mmmm	CGAGCUAAAUUCU	543
CTGF-1048-16-14039	14039	Chl	oooooooooooo o	mmm0m0000m0m0	UCUGUGGAGUAUG	544
CTGF-1235-16-14040	14040	Chl	oooooooooooo o	m0000m0m00m0	CGGAGACAUGGCA	545
CTGF-868-16-14041	14041	Chl	oooooooooooo o	0m00m00mmmmm	AUGACAACGCCUC	546
CTGF-1131-16-14042	14042	Chl	oooooooooooo o	0000mm0m00000	GAGGUCAUGAAGA	547
CTGF-1043-16-14043	14043	Chl	oooooooooooo o	m000mmmm0m000	UAAAUUCUGUGGA	548
CTGF-751-16-14044	14044	Chl	oooooooooooo o	m000000m0mmm	UGGAAGACACGUU	549
CTGF-1227-16-14045	14045	Chl	oooooooooooo o	0000m0m0m000	AAGAUGUACGGAG	550
CTGF-867-16-14046	14046	Chl	oooooooooooo o	00m00m00mmmm	AAUGACAACGCCU	551
CTGF-1128-16-14047	14047	Chl	oooooooooooo o	00m000mm0m00	GGCGAGGUCAUGA	552
CTGF-756-16-14048	14048	Chl	oooooooooooo o	00m0m0mmm00mm	GACACGUUUGGCC	553

TABLE 3-continued

Sense backbone, chemistry, and sequence information. o: phosphodiester; s: phosphorothioate; P: 5'phosphorylation; 0: 2'-OH; F: 2'-fluoro; m: 2'O-methyl; +: LNA modification. Capital letters in the sequence signify ribonucleotides, lower case letters signify deoxyribonucleotides.

ID Number	Oligo Number	OHang Sense Chem.	Sense Backbone	Sense Chemistry	Sense Sequence	SEQ ID NO:
CTGF-1234-16-14049	14049	Chl	ooooooooooooo	0m00000m0m00m	ACGGAGACAUGGC	554
CTGF-916-16-14050	14050	Chl	ooooooooooooo	mm000mmmm0m00	UCAGGCCUUGCGA	555
CTGF-925-16-14051	14051	Chl	ooooooooooooo	0m0000mm00mmm	GCGAAGCUGACCU	556
CTGF-1225-16-14052	14052	Chl	ooooooooooooo	000000m0m0m00	GGAAGAUGUACGG	557
CTGF-445-16-14053	14053	Chl	ooooooooooooo	0m00mmmm00mmm	GUGACUUCGGCUC	558
CTGF-446-16-14054	14054	Chl	ooooooooooooo	m00mmmm00mmmm	UGACUUCGGCUCC	559
CTGF-913-16-14055	14055	Chl	ooooooooooooo	m00mm000mmmm0	UGGUCAGGCCUUG	560
CTGF-997-16-14056	14056	Chl	ooooooooooooo	mm000mmm000mm	UCAAGUUUGAGCU	561
CTGF-277-16-14057	14057	Chl	ooooooooooooo	0mm0000mm0m00	GCCAGAACUGCAG	562
CTGF-1052-16-14058	14058	Chl	ooooooooooooo	m0000m0m0m0mm	UGGAGUAUGUACC	563
CTGF-887-16-14059	14059	Chl	ooooooooooooo	0mm0000000m00	GCUAGAGAAGCAG	564
CTGF-914-16-14060	14060	Chl	ooooooooooooo	00mm000mmmm0m	GGUCAGGCCUUGC	565
CTGF-1039-16-14061	14061	Chl	ooooooooooooo	000mm000mmmm0	GAGCUAAAUUCUG	566
CTGF-754-16-14062	14062	Chl	ooooooooooooo	000m0m0mmm00	AAGACACGUUUGG	567
CTGF-1130-16-14063	14063	Chl	ooooooooooooo	m0000mm0m0000	CGAGGUCAUGAAG	568
CTGF-919-16-14064	14064	Chl	ooooooooooooo	00mmmm0m0000m	GGCCUUGCGAAGC	569
CTGF-922-16-14065	14065	Chl	ooooooooooooo	mmm0m0000mm00	CUUGCGAAGCUGA	570
CTGF-746-16-14066	14066	Chl	ooooooooooooo	mm00mm000000m	CCGACUGGAAGAC	571
CTGF-993-16-14067	14067	Chl	ooooooooooooo	mmm0mm000mmm0	CCUAUCAAGUUUG	572
CTGF-825-16-14068	14068	Chl	ooooooooooooo	m0mmmm0000mmm	UGUUCCAAGACCU	573
CTGF-926-16-14069	14069	Chl	ooooooooooooo	m0000mm00mmm0	CGAAGCUGACCUG	574
CTGF-923-16-14070	14070	Chl	ooooooooooooo	mm0m0000mm00m	UUGCGAAGCUGAC	575
CTGF-866-16-14071	14071	Chl	ooooooooooooo	m00m00m00m0mm	CAAUGACAACGCC	576
CTGF-563-16-14072	14072	Chl	ooooooooooooo	0m0mm00m0m0m0	GUACCAGUGCACG	577

TABLE 3-continued

Sense backbone, chemistry, and sequence information. o: phosphodiester; s: phosphorothioate; P: 5'phosphorylation; 0: 2'-OH; F: 2'-fluoro; m: 2'O-methyl; +: LNA modification. Capital letters in the sequence signify ribonucleotides, lower case letters signify deoxyribonucleotides.

ID Number	Oligo Number	OHang Sense Chem.	Sense Backbone	Sense Chemistry	Sense Sequence	SEQ ID NO:
CTGF-823-16-14073	14073	Chl	ooooooooooooo	mmm0mmmm0000m	CCUGUUCCAAGAC	578
CTGF-1233-16-14074	14074	Chl	ooooooooooooo	m0m00000m0m00	UACGGAGACAUGG	579
CTGF-924-16-14075	14075	Chl	ooooooooooooo	m0m0000mm00mm	UGCGAAGCUGACC	580
CTGF-921-16-14076	14076	Chl	ooooooooooooo	mmmm0m0000mm0	CCUUGCGAAGCUG	581
CTGF-443-16-14077	14077	Chl	ooooooooooooo	mm0m00mmmm00m	CUGUGACUUCGGC	582
CTGF-1041-16-14078	14078	Chl	ooooooooooooo	0mm000mmmm0m0	GCUAAAUUCUGUG	583
CTGF-1042-16-14079	14079	Chl	ooooooooooooo	mm000mmmm0m00	CUAAAUUCUGUGG	584
CTGF-755-16-14080	14080	Chl	ooooooooooooo	000m0m0mmm00m	AGACACGUUUGGC	585
CTGF-467-16-14081	14081	Chl	ooooooooooooo	mm0m0000mm00m	CCGCAAGAUCGGC	586
CTGF-995-16-14082	14082	Chl	ooooooooooooo	m0mm000mmm000	UAUCAAGUUUGAG	587
CTGF-927-16-14083	14083	Chl	ooooooooooooo	0000mm00mmm00	GAAGCUGACCUGG	588
SPP1-1091-16-14131	14131	Chl	ooooooooooooo	0m0mmm00mm000	GCAUUUAGUCAAA	589
PPIB--16-14188	14188	Chl	ooooooooooooo	mmmmmmmmmmmmm	GGCUACAAAAACA	590
PPIB--17-14189	14189	Chl	ooooooooooooooo	mm00mm0m00000m0	UUGGCUACAAAAACA	591
PPIB--18-14190	14190	Chl	ooooooooooooooooo	0mmm00mm0m00000m0	AUUUGGCUACAAAAACA	592
pGL3-1172-16-14386	14386	chl	ooooooooooooo	0m000m0m00mmm	ACAAAUACGAUUU	593
pGL3-1172-16-14387	14387	chl	ooooooooooooo	DY5470m000m0m00mmm	ACAAAUACGAUUU	594
MAP4K4-2931-25-14390	14390	Chl	ooooooooooooooooooooooooo	Pmmmmmmmmmmmm000mmmmmmmmmm	CUUUGAAGAGUUCUGUGGAAGUCUA	595
miR-122--23-14391	14391	Chl	ssooooooooooooooooossss	mmmmmmmmmmmmmmmmmmmmmmm	ACAAACACCAUUGUCACACUCCA	596
	14084	Chl	ooooooooooooo	mmm0m000mm000	CUCAUGAAUUAGA	719
	14085	Chl	ooooooooooooo	mm0000mm00mm0	CUGAGGUCAAUUA	720
	14086	Chl	ooooooooooooo	0000mm00mm000	GAGGUCAAUUAAA	721
	14087	Chl	ooooooooooooo	mmm0000mm00mm	UCUGAGGUCAAUU	722

TABLE 3-continued

Sense backbone, chemistry, and sequence information. o: phosphodiester; s: phosphorothioate; P: 5'phosphorylation; 0: 2'-OH; F: 2'-fluoro; m: 2'O-methyl; +: LNA modification. Capital letters in the sequence signify ribonucleotides, lower case letters signify deoxyribonucleotides.

ID Number	Oligo Number	OHang Sense Chem.	Sense Backbone	Sense Chemistry	Sense Sequence	SEQ ID NO:
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	14090	Chl	ooooooooooooo	0mm00mm000m00	GUCAGCUGGAUGA	725
	14091	Chl	ooooooooooooo	mmmm00m000mmm	UUCUGAUGAAUCU	726
	14092	Chl	ooooooooooooo	m000mm0000mm0	UGGACUGAGGUCA	727
	14093	Chl	ooooooooooooo	000mmmm0mm0mm	GAGUCUCACCAUU	728
	14094	Chl	ooooooooooooo	00mm0000mm000	GACUGAGGUCAAA	729
	14095	Chl	ooooooooooooo	mm0m00mm0m000	UCACAGCCAUGAA	730
	14096	Chl	ooooooooooooo	00mmmm0mm0mmm	AGUCUCACCAUUC	731
	14097	Chl	ooooooooooooo	000m00000mm0	AAGCGGAAAGCCA	732
	14098	Chl	ooooooooooooo	00m00000mm00	AGCGGAAAGCCAA	733
	14099	Chl	ooooooooooooo	0mm0m0m000m00	ACCACAUGGAUGA	734
	14100	Chl	ooooooooooooo	0mm0m00mm0m0m	GCCAUGACCACAU	735
	14101	Chl	ooooooooooooo	000mm0m00mm0m	AAGCCAUGACCAC	736
	14102	Chl	ooooooooooooo	0m00000mm00m	GCGGAAAGCCAAU	737
	14103	Chl	ooooooooooooo	000mmmmm0mmm	AAAUUUCGUAUUU	738
	14104	Chl	ooooooooooooo	0mmmmm0mmmmm	AUUUCGUAUUUCU	739
	14105	Chl	ooooooooooooo	0000mm0m00mm0	AAAGCCAUGACCA	740
	14106	Chl	ooooooooooooo	0m0m000m00m0m	ACAUGGAUGAUAU	741
	14107	Chl	ooooooooooooo	0000mmmmm0mm	GAAAUUUCGUAUU	742
	14108	Chl	ooooooooooooo	0mmmmmmm00mm	GCGCCUUCUGAUU	743
	14109	Chl	ooooooooooooo	0mmmmmm0m000m	AUUUCUCAUGAAU	744
	14110	Chl	ooooooooooooo	mmmmm0m000m00	CUCUCAUGAAUAG	745
	14111	Chl	ooooooooooooo	000mmm00m000	AAGUCCAACGAAA	746

TABLE 3-continued

Sense backbone, chemistry, and sequence information. o: phosphodiester; s: phosphorothioate; P: 5'phosphorylation; 0: 2'-OH; F: 2'-fluoro; m: 2'O-methyl; +: LNA modification. Capital letters in the sequence signify ribonucleotides, lower case letters signify deoxyribonucleotides.

ID Number	Oligo Number	OHang Sense Chem.	Sense Backbone	Sense Chemistry	Sense Sequence	SEQ ID NO:
	14112	Chl	oooooooooooo o	0m00m00000m00	AUGAUGAGAGCAA	747
	14113	Chl	oooooooooooo o	0m00000mm000	GCGAGGAGUUGAA	748
	14114	Chl	oooooooooooo o	m00mm00m00mm0	UGAUUGAUAGUCA	749
	14115	Chl	oooooooooooo o	000m00m0m0mmm	AGAUAGUGCAUCU	750
	14116	Chl	oooooooooooo o	0m0m0m0mmm0mm	AUGUGUAUCUAUU	751
	14117	Chl	oooooooooooo o	mmmm0m0000000	UUCUAUAGAAGAA	752
	14118	Chl	oooooooooooo o	mm0mmm00m00mm	UUGUCCAGCAAUU	753
	14119	Chl	oooooooooooo o	0m0m000000m0	ACAUGGAAAGCGA	754
	14120	Chl	oooooooooooo o	0m00mmm000mm0	GCAGUCCAGAUUA	755
	14121	Chl	oooooooooooo o	m00mm000m0m0m	UGGUUGAAUGUGU	756
	14122	Chl	oooooooooooo o	mm0m0000m00m	UUAUGAAACGAGU	757
	14123	Chl	oooooooooooo o	m00mmm000mm0m	CAGUCCAGAUUAU	758
	14124	Chl	oooooooooooo o	0m0m000m0000	AUAUAAGCGGAAA	759
	14125	Chl	oooooooooooo o	m0mm00mm000m0	UACCAGUUAAACA	760
	14126	Chl	oooooooooooo o	m0mmm0mmmm0m0	UGUUCAUUCUAUA	761
	14127	Chl	oooooooooooo o	mm0mm0000000	CCGACCAAGGAAA	762
	14128	Chl	oooooooooooo o	000m00m0m0m0m	GAAUGGUGCAUAC	763
	14129	Chl	oooooooooooo o	0m0m00m00mm0	AUAUGAUGGCCGA	764
	14130	Chl	oooooooooooo o	00m00mmm000mm	AGCAGUCCAGAUU	765
	14132	Chl	oooooooooooo o	00m0mmmm0m0m	AGCAUUCCGAUGU	766
	14133	Chl	oooooooooooo o	m00mm00000mmm	UAGUCAGGAACUU	767
	14134	Chl	oooooooooooo o	m0m0mmm00mm00	UGCAUUUAGUCAA	768
	14135	Chl	oooooooooooo o	0mmm00m000mmm	GUCUGAUGAGUCU	769
	14136	Chl	oooooooooooo o	m000m0m0m0m00	UAGACACAUAUGA	770

TABLE 3-continued

Sense backbone, chemistry, and sequence information. o: phosphodiester; s: phosphorothioate; P: 5'phosphorylation; 0: 2'-OH; F: 2'-fluoro; m: 2'O-methyl; +: LNA modification. Capital letters in the sequence signify ribonucleotides, lower case letters signify deoxyribonucleotides.

ID Number	Oligo Number	OHang Sense Chem.	Sense Backbone	Sense Chemistry	Sense Sequence	SEQ ID NO:
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	14139	Chl	oooooooooooo o	00mmm00000m00	AGUCUGGAAAUAA	773
	14140	Chl	oooooooooooo o	00mmm0m00mmmm	AGUUUGUGGCUUC	774
	14141	Chl	oooooooooooo o	00mmm00m0000	AGUCCAACGAAAG	775
	14142	Chl	oooooooooooo o	000mmmmm000m	AAGUUUCGCAGAC	776
	14143	Chl	oooooooooooo o	00m00m000m0mm	AGCAAUGAGCAUU	777
	14144	Chl	oooooooooooo o	mm000m00m0m0m	UUAGAUAGUGCAU	778
	14145	Chl	oooooooooooo o	m00m0m0m0m000	UGGUGCAUACAAG	779
	14146	Chl	oooooooooooo o	0m0000m00mm0	AUGAAACGAGUCA	780
	14147	Chl	oooooooooooo o	mm0000m0mm000	CCAGAGUGCUGAA	781
	14148	Chl	oooooooooooo o	m00mm0m000mmm	CAGCCAUGAAUUU	782
	14149	Chl	oooooooooooo o	0mm00mm000m0m	AUUGGUUGAAUGU	783
	14150	Chl	oooooooooooo o	00mm000m0m0m0	GGUUGAAUGUGUA	784
	14151	Chl	oooooooooooo o	00000m00mm00m	GGAAAUAACUAAU	785
	14152	Chl	oooooooooooo o	mm0m000m00000	UCAUGAAUAGAAA	786
	14153	Chl	oooooooooooo o	0mm00m00mm00	GCCAGCAACCGAA	787
	14154	Chl	oooooooooooo o	m0mmmm0m0m0m0	CACCUCACACAUG	788
	14155	Chl	oooooooooooo o	00mm000m00m0m	AGUUGAAUGGUGC	789
	14156	Chl	oooooooooooo o	00mm00mm000m0	AGUCAGCUGGAUG	790
	14157	Chl	oooooooooooo o	m0m000m00000	UAUAAGCGGAAAG	791
	14158	Chl	oooooooooooo o	mmmm0m0m00mm	UUCCGAUGUGAUU	792
	14159	Chl	oooooooooooo o	0m00mm00m0m0m	AUAACUAAUGUGU	793
	14160	Chl	oooooooooooo o	mm0mmmm0m0000	UCAUUCUAUAGAA	794

TABLE 3-continued

Sense backbone, chemistry, and sequence information. o: phosphodiester; s: phosphorothioate; P: 5'phosphorylation; 0: 2'-OH; F: 2'-fluoro; m: 2'O-methyl; +: LNA modification. Capital letters in the sequence signify ribonucleotides, lower case letters signify deoxyribonucleotides.

ID Number	Oligo Number	OHang Sense Chem.	Sense Backbone	Sense Chemistry	Sense Sequence	SEQ ID NO:
	14161	Chl	ooooooooooooo	00mm0mm0mm0m0	AACUAUCACUGUA	795
	14162	Chl	ooooooooooooo	0mm00mm0mmm0m	GUCAAUUGCUUAU	796
	14163	Chl	ooooooooooooo	00m00mm00m000	AGCAAUUAAUAAA	797
	14164	Chl	ooooooooooooo	0m0mmmm00m00	ACGACUCUGAUGA	798
	14165	Chl	ooooooooooooo	m00m0m00mmm0m	UAGUGUGGUUUAU	799
	14166	Chl	ooooooooooooo	000mm00m00m00	AAGCCAAUGAUGA	800
	14167	Chl	ooooooooooooo	0m00mm00000mm	AUAGUCAGGAACU	801
	14168	Chl	ooooooooooooo	00mm00mmm000	AGUCAGCCGUGAA	802
	14169	Chl	ooooooooooooo	0mm0mm0m00000	ACUACCAUGAGAA	803
	14170	Chl	ooooooooooooo	000m000mm00mm	AAACAGGCUGAUU	804
	14171	Chl	ooooooooooooo	000m0mm0000mm	GAGUGCUGAAACC	805
	14172	Chl	ooooooooooooo	m000m0mmmm0m	UGAGCAUUCCGAU	806
	14173	Chl	ooooooooooooo	00mmmm0m00mm0	AAUUCCACAGCCA	807
	14174	Chl	ooooooooooooo	m0mm00mm0mmm0	UGUCAAUUGCUUA	808
	14175	Chl	ooooooooooooo	0mm0m00000mm0	ACCAUGAGAAUUG	809
	14176	Chl	ooooooooooooo	mm00m0000mm0	CCAACGAAAGCCA	810
	14177	Chl	ooooooooooooo	mm00mm0mm00mm	CUGGUCACUGAUU	811
	14178	Chl	ooooooooooooo	m00mmm0m000mm	UGGUUUAUGGACU	812
	14179	Chl	ooooooooooooo	00mm0000m0mm0	GACCAGAGUGCUG	813
	14180	Chl	ooooooooooooo	00m0m00mm00m0	GAUGUGAUUGAUA	814
	14181	Chl	ooooooooooooo	0mm00mmm000m	GUCAGCCGUGAAU	815
	14182	Chl	ooooooooooooo	00m0m0m0mmm0m	AAUGUGUAUCUAU	816
	14183	Chl	ooooooooooooo	mm000mmm00000	UUGAGUCUGGAAA	817
	14184	Chl	ooooooooooooo	0mmm00m00mm00	GUCCAGCAAUUAA	818

TABLE 3-continued

Sense backbone, chemistry, and sequence information. o: phosphodiester; s: phosphorothioate; P: 5'phosphorylation; 0: 2'-OH; F: 2'-fluoro; m: 2'O-methyl; +: LNA modification. Capital letters in the sequence signify ribonucleotides, lower case letters signify deoxyribonucleotides.

ID Number	Oligo Number	OHang Sense Chem.	Sense Backbone	Sense Chemistry	Sense Sequence	SEQ ID NO:
	14185	Chl	ooooooooooooo	mm00m00mm00m0	CCAGCAAUUAAUA	819
	14186	Chl	ooooooooooooo	00mmm00m0mm	GACUCGAACGACU	820
	14187	Chl	ooooooooooooo	0mmm0mm00m00m	ACCUGCCAGCAAC	821

Having thus described several aspects of at least one embodiment of this invention, it is to be appreciated various alterations, modifications, and improvements will readily occur to those skilled in the art. Such alterations, modifications, and improvements are intended to be part of this disclosure, and are intended to be within the spirit and scope of the invention. Accordingly, the foregoing description and drawings are by way of example only.

EQUIVALENTS

Those skilled in the art will recognize, or be able to ascertain using no more than routine experimentation, many equivalents to the specific embodiments of the invention described herein. Such equivalents are intended to be encompassed by the following claims.

All references, including patent documents, disclosed herein are incorporated by reference in their entirety. This application incorporates by reference the entire contents, including all the drawings and all parts of the specification (including sequence listing or amino acid/polynucleotide sequences) of the co-pending U.S. Provisional Application No. 61/135,855, filed on Jul. 24, 2008, entitled "SHORT HAIRPIN RNAI CONSTRUCTS AND USES THEREOF," and U.S. Provisional Application No. 61/197,768, filed on Oct. 30, 2008, entitled "MINIRNA CONSTRUCTS AND USES THEREOF."

SEQUENCE LISTING

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auugguauuc agugugauga c 21

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auugguauuc agugugauga c 21

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<223> OTHER INFORMATION: synthetic oligonucleotide

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uagacuucca cagaacucu 19

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uagacuucca cagaacucu 19

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uacuuucuuc auuuccacc 19

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uagacuucca cagaacucu 19

<210> SEQ ID NO 49
<211> LENGTH: 19
<212> TYPE: RNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: synthetic oligonucleotide

<400> SEQUENCE: 49

uagacuucca cagaacucu 19

<210> SEQ ID NO 50
<211> LENGTH: 19
<212> TYPE: RNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: synthetic oligonucleotide

<400> SEQUENCE: 50

uagacauccu acacagcac 19

<210> SEQ ID NO 51
<211> LENGTH: 19
<212> TYPE: RNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: synthetic oligonucleotide

<400> SEQUENCE: 51

uguuucucca gauccuugc 19

<210> SEQ ID NO 52
<211> LENGTH: 19
<212> TYPE: RNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: synthetic oligonucleotide

<400> SEQUENCE: 52

uguuucucca gauccuugc 19

<210> SEQ ID NO 53
<211> LENGTH: 19
<212> TYPE: RNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: synthetic oligonucleotide

<400> SEQUENCE: 53

uagcagauga guccauuug 19

<210> SEQ ID NO 54
<211> LENGTH: 23
<212> TYPE: RNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: synthetic oligonucleotide

<400> SEQUENCE: 54

uagcagauga guccauuugg aga 23

<210> SEQ ID NO 55
<211> LENGTH: 19
<212> TYPE: RNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: synthetic oligonucleotide

<400> SEQUENCE: 55

uagcagauga guccauuug 19

<210> SEQ ID NO 56
<211> LENGTH: 23
<212> TYPE: RNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: synthetic oligonucleotide

<400> SEQUENCE: 56

uagcagauga guccauuugg aga 23

<210> SEQ ID NO 57
<211> LENGTH: 19
<212> TYPE: RNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: synthetic oligonucleotide

<400> SEQUENCE: 57

auguuguuuc uccagaucc 19

<210> SEQ ID NO 58
<211> LENGTH: 19
<212> TYPE: RNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: synthetic oligonucleotide

<400> SEQUENCE: 58

auguuguuuc uccagaucc 19

<210> SEQ ID NO 59
<211> LENGTH: 19
<212> TYPE: RNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: synthetic oligonucleotide

<400> SEQUENCE: 59

uguuugaggg acucuguga 19

<210> SEQ ID NO 60
<211> LENGTH: 19
<212> TYPE: RNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: synthetic oligonucleotide

<400> SEQUENCE: 60

uguuugaggg acucuguga 19

<210> SEQ ID NO 61
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<212> TYPE: RNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: synthetic oligonucleotide

<400> SEQUENCE: 61

auugguauuc agugugaug 19

<210> SEQ ID NO 62
<211> LENGTH: 23
<212> TYPE: RNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: synthetic oligonucleotide

<400> SEQUENCE: 62

auugguauuc agugugauga cac 23

<210> SEQ ID NO 63
<211> LENGTH: 19

<212> TYPE: RNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: synthetic oligonucleotide

<400> SEQUENCE: 63

auugguauuc agugugaug 19

<210> SEQ ID NO 64
<211> LENGTH: 23
<212> TYPE: RNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: synthetic oligonucleotide

<400> SEQUENCE: 64

auugguauuc agugugauga cac 23

<210> SEQ ID NO 65
<211> LENGTH: 19
<212> TYPE: RNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: synthetic oligonucleotide

<400> SEQUENCE: 65

uagacuucca cagaacucu 19

<210> SEQ ID NO 66
<211> LENGTH: 19
<212> TYPE: RNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: synthetic oligonucleotide

<400> SEQUENCE: 66

uacaucuucc uguaguaca 19

<210> SEQ ID NO 67
<211> LENGTH: 19
<212> TYPE: RNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: synthetic oligonucleotide

<400> SEQUENCE: 67

aggcgcucca cucuguggu 19

<210> SEQ ID NO 68
<211> LENGTH: 19
<212> TYPE: RNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: synthetic oligonucleotide

<400> SEQUENCE: 68

ugucuuccag ucgguaagc 19

<210> SEQ ID NO 69
<211> LENGTH: 19
<212> TYPE: RNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: synthetic oligonucleotide

<400> SEQUENCE: 69

gaacaggcgc uccacucug 19

<210> SEQ ID NO 70
<211> LENGTH: 19
<212> TYPE: RNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: synthetic oligonucleotide

<400> SEQUENCE: 70

caguuguaau ggcaggcac 19

<210> SEQ ID NO 71
<211> LENGTH: 19
<212> TYPE: RNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: synthetic oligonucleotide

<400> SEQUENCE: 71

agccagaaag cucaaacuu 19

<210> SEQ ID NO 72
<211> LENGTH: 19
<212> TYPE: RNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: synthetic oligonucleotide

<400> SEQUENCE: 72

caggcgcucc acucugugg 19

<210> SEQ ID NO 73
<211> LENGTH: 19
<212> TYPE: RNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: synthetic oligonucleotide

<400> SEQUENCE: 73

aacaggcgcu ccacucugu 19

<210> SEQ ID NO 74
<211> LENGTH: 19
<212> TYPE: RNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: synthetic oligonucleotide

<400> SEQUENCE: 74

agaaagcuca aacuugaua 19

<210> SEQ ID NO 75
<211> LENGTH: 19
<212> TYPE: RNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: synthetic oligonucleotide

<400> SEQUENCE: 75

aguuguaaug gcaggcaca 19

<210> SEQ ID NO 76
<211> LENGTH: 19
<212> TYPE: RNA
<213> ORGANISM: Artificial Sequence

<220> FEATURE:
<223> OTHER INFORMATION: synthetic oligonucleotide

<400> SEQUENCE: 76

cgugucuucc agucgguaa 19

<210> SEQ ID NO 77
<211> LENGTH: 19
<212> TYPE: RNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: synthetic oligonucleotide

<400> SEQUENCE: 77

ggaccaggca guuggcucu 19

<210> SEQ ID NO 78
<211> LENGTH: 19
<212> TYPE: RNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: synthetic oligonucleotide

<400> SEQUENCE: 78

caggcacagg ucuugauga 19

<210> SEQ ID NO 79
<211> LENGTH: 19
<212> TYPE: RNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: synthetic oligonucleotide

<400> SEQUENCE: 79

gcgcuccacu cuguggucu 19

<210> SEQ ID NO 80
<211> LENGTH: 19
<212> TYPE: RNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: synthetic oligonucleotide

<400> SEQUENCE: 80

ggucuggacc aggcaguug 19

<210> SEQ ID NO 81
<211> LENGTH: 19
<212> TYPE: RNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: synthetic oligonucleotide

<400> SEQUENCE: 81

acaguuguaa uggcaggca 19

<210> SEQ ID NO 82
<211> LENGTH: 19
<212> TYPE: RNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: synthetic oligonucleotide

<400> SEQUENCE: 82

guuguaaugg caggcacag 19

<210> SEQ ID NO 83
<211> LENGTH: 19
<212> TYPE: RNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: synthetic oligonucleotide

<400> SEQUENCE: 83

ggacaguugu aauggcagg 19

<210> SEQ ID NO 84
<211> LENGTH: 19
<212> TYPE: RNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: synthetic oligonucleotide

<400> SEQUENCE: 84

gacaguugua auggcaggc 19

<210> SEQ ID NO 85
<211> LENGTH: 19
<212> TYPE: RNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: synthetic oligonucleotide

<400> SEQUENCE: 85

ggcgcuccac ucugugguc 19

<210> SEQ ID NO 86
<211> LENGTH: 19
<212> TYPE: RNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: synthetic oligonucleotide

<400> SEQUENCE: 86

ucuuccaguc gguaagccg 19

<210> SEQ ID NO 87
<211> LENGTH: 19
<212> TYPE: RNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: synthetic oligonucleotide

<400> SEQUENCE: 87

ugucuccgua caucuuccu 19

<210> SEQ ID NO 88
<211> LENGTH: 19
<212> TYPE: RNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: synthetic oligonucleotide

<400> SEQUENCE: 88

agcuucgcaa ggccugacc 19

<210> SEQ ID NO 89
<211> LENGTH: 19
<212> TYPE: RNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: synthetic oligonucleotide

<400> SEQUENCE: 89

cacuccucgc agcauuucc 19

<210> SEQ ID NO 90
<211> LENGTH: 19
<212> TYPE: RNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: synthetic oligonucleotide

<400> SEQUENCE: 90

aaacuugaua ggcuuggag 19

<210> SEQ ID NO 91
<211> LENGTH: 19
<212> TYPE: RNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: synthetic oligonucleotide

<400> SEQUENCE: 91

acuccacaga auuuagcuc 19

<210> SEQ ID NO 92
<211> LENGTH: 19
<212> TYPE: RNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: synthetic oligonucleotide

<400> SEQUENCE: 92

augucuccgu acaucuucc 19

<210> SEQ ID NO 93
<211> LENGTH: 19
<212> TYPE: RNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: synthetic oligonucleotide

<400> SEQUENCE: 93

aacuugauag gcuuggaga 19

<210> SEQ ID NO 94
<211> LENGTH: 19
<212> TYPE: RNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: synthetic oligonucleotide

<400> SEQUENCE: 94

aagcucaaac uugauaggc 19

<210> SEQ ID NO 95
<211> LENGTH: 19
<212> TYPE: RNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: synthetic oligonucleotide

<400> SEQUENCE: 95

acauacucca cagaauuua 19

<210> SEQ ID NO 96

<211> LENGTH: 19
<212> TYPE: RNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: synthetic oligonucleotide

<400> SEQUENCE: 96

cuccacagaa uuuagcucg 19

<210> SEQ ID NO 97
<211> LENGTH: 19
<212> TYPE: RNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: synthetic oligonucleotide

<400> SEQUENCE: 97

ugugcuacug aaaucauuu 19

<210> SEQ ID NO 98
<211> LENGTH: 19
<212> TYPE: RNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: synthetic oligonucleotide

<400> SEQUENCE: 98

aaagauguca uugucuccg 19

<210> SEQ ID NO 99
<211> LENGTH: 19
<212> TYPE: RNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: synthetic oligonucleotide

<400> SEQUENCE: 99

gugcacuggu acuugcagc 19

<210> SEQ ID NO 100
<211> LENGTH: 19
<212> TYPE: RNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: synthetic oligonucleotide

<400> SEQUENCE: 100

aaacgugucu uccagucgg 19

<210> SEQ ID NO 101
<211> LENGTH: 19
<212> TYPE: RNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: synthetic oligonucleotide

<400> SEQUENCE: 101

ucaaacuuga uaggcuugg 19

<210> SEQ ID NO 102
<211> LENGTH: 19
<212> TYPE: RNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: synthetic oligonucleotide

<400> SEQUENCE: 102

acagaauuua gcucgguau 19

<210> SEQ ID NO 103
<211> LENGTH: 19
<212> TYPE: RNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: synthetic oligonucleotide

<400> SEQUENCE: 103

uuacauucua ccuauggug 19

<210> SEQ ID NO 104
<211> LENGTH: 19
<212> TYPE: RNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: synthetic oligonucleotide

<400> SEQUENCE: 104

aaacugauca gcuauauag 19

<210> SEQ ID NO 105
<211> LENGTH: 19
<212> TYPE: RNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: synthetic oligonucleotide

<400> SEQUENCE: 105

uaucugagca gaauuucca 19

<210> SEQ ID NO 106
<211> LENGTH: 19
<212> TYPE: RNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: synthetic oligonucleotide

<400> SEQUENCE: 106

uuaacuuaga uaacuguac 19

<210> SEQ ID NO 107
<211> LENGTH: 19
<212> TYPE: RNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: synthetic oligonucleotide

<400> SEQUENCE: 107

uauuacucgu auaagaugc 19

<210> SEQ ID NO 108
<211> LENGTH: 19
<212> TYPE: RNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: synthetic oligonucleotide

<400> SEQUENCE: 108

aagcugucca gucuaaucg 19

<210> SEQ ID NO 109
<211> LENGTH: 19
<212> TYPE: RNA

<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: synthetic oligonucleotide

<400> SEQUENCE: 109

uaauaaaggc cauuuguuc 19

<210> SEQ ID NO 110
<211> LENGTH: 19
<212> TYPE: RNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: synthetic oligonucleotide

<400> SEQUENCE: 110

uuuagcucgg uaugucuuc 19

<210> SEQ ID NO 111
<211> LENGTH: 19
<212> TYPE: RNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: synthetic oligonucleotide

<400> SEQUENCE: 111

acacucucaa caaauaaac 19

<210> SEQ ID NO 112
<211> LENGTH: 19
<212> TYPE: RNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: synthetic oligonucleotide

<400> SEQUENCE: 112

uagcucggua ugucuucau 19

<210> SEQ ID NO 113
<211> LENGTH: 19
<212> TYPE: RNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: synthetic oligonucleotide

<400> SEQUENCE: 113

uaaccuuucu gcugguacc 19

<210> SEQ ID NO 114
<211> LENGTH: 19
<212> TYPE: RNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: synthetic oligonucleotide

<400> SEQUENCE: 114

uuaaggaaca acuugacuc 19

<210> SEQ ID NO 115
<211> LENGTH: 19
<212> TYPE: RNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: synthetic oligonucleotide

<400> SEQUENCE: 115

uuacacuuca aauagcagg 19

<210> SEQ ID NO 116
<211> LENGTH: 19
<212> TYPE: RNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: synthetic oligonucleotide

<400> SEQUENCE: 116

uccaggucag cuucgcaag 19

<210> SEQ ID NO 117
<211> LENGTH: 19
<212> TYPE: RNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: synthetic oligonucleotide

<400> SEQUENCE: 117

cuucuucaug accucgccg 19

<210> SEQ ID NO 118
<211> LENGTH: 19
<212> TYPE: RNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: synthetic oligonucleotide

<400> SEQUENCE: 118

aaggccugac caugcacag 19

<210> SEQ ID NO 119
<211> LENGTH: 19
<212> TYPE: RNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: synthetic oligonucleotide

<400> SEQUENCE: 119

caaacguguc uuccagucg 19

<210> SEQ ID NO 120
<211> LENGTH: 19
<212> TYPE: RNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: synthetic oligonucleotide

<400> SEQUENCE: 120

cuucgcaagg ccugaccau 19

<210> SEQ ID NO 121
<211> LENGTH: 19
<212> TYPE: RNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: synthetic oligonucleotide

<400> SEQUENCE: 121

cuuccagucg guaagccgc 19

<210> SEQ ID NO 122
<211> LENGTH: 19
<212> TYPE: RNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:

<223> OTHER INFORMATION: synthetic oligonucleotide

<400> SEQUENCE: 122

ccgaucuugc gguuggccg 19

<210> SEQ ID NO 123
<211> LENGTH: 19
<212> TYPE: RNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: synthetic oligonucleotide

<400> SEQUENCE: 123

uucgcaaggc cugaccaug 19

<210> SEQ ID NO 124
<211> LENGTH: 19
<212> TYPE: RNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: synthetic oligonucleotide

<400> SEQUENCE: 124

agaauuuagc ucgguaugu 19

<210> SEQ ID NO 125
<211> LENGTH: 19
<212> TYPE: RNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: synthetic oligonucleotide

<400> SEQUENCE: 125

cauacuccac agaauuuag 19

<210> SEQ ID NO 126
<211> LENGTH: 19
<212> TYPE: RNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: synthetic oligonucleotide

<400> SEQUENCE: 126

ugccaugucu ccguacauc 19

<210> SEQ ID NO 127
<211> LENGTH: 19
<212> TYPE: RNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: synthetic oligonucleotide

<400> SEQUENCE: 127

gaggcguugu cauugguaa 19

<210> SEQ ID NO 128
<211> LENGTH: 19
<212> TYPE: RNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: synthetic oligonucleotide

<400> SEQUENCE: 128

ucuucaugac cucgccguc 19

<210> SEQ ID NO 129
<211> LENGTH: 19
<212> TYPE: RNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: synthetic oligonucleotide

<400> SEQUENCE: 129

uccacagaau uuagcucgg 19

<210> SEQ ID NO 130
<211> LENGTH: 19
<212> TYPE: RNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: synthetic oligonucleotide

<400> SEQUENCE: 130

aacgugucuu ccagucggu 19

<210> SEQ ID NO 131
<211> LENGTH: 19
<212> TYPE: RNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: synthetic oligonucleotide

<400> SEQUENCE: 131

cuccguacau cuuccugua 19

<210> SEQ ID NO 132
<211> LENGTH: 19
<212> TYPE: RNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: synthetic oligonucleotide

<400> SEQUENCE: 132

aggcguuguc auugguaac 19

<210> SEQ ID NO 133
<211> LENGTH: 19
<212> TYPE: RNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: synthetic oligonucleotide

<400> SEQUENCE: 133

ucaugaccuc gccgucagg 19

<210> SEQ ID NO 134
<211> LENGTH: 19
<212> TYPE: RNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: synthetic oligonucleotide

<400> SEQUENCE: 134

ggccaaacgu gucuuccag 19

<210> SEQ ID NO 135
<211> LENGTH: 19
<212> TYPE: RNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: synthetic oligonucleotide

<400> SEQUENCE: 135

gccaugucuc cguacaucu 19

<210> SEQ ID NO 136
<211> LENGTH: 19
<212> TYPE: RNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: synthetic oligonucleotide

<400> SEQUENCE: 136

ucgcaaggcc ugaccaugc 19

<210> SEQ ID NO 137
<211> LENGTH: 19
<212> TYPE: RNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: synthetic oligonucleotide

<400> SEQUENCE: 137

aggucagcuu cgcaaggcc 19

<210> SEQ ID NO 138
<211> LENGTH: 19
<212> TYPE: RNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: synthetic oligonucleotide

<400> SEQUENCE: 138

ccguacaucu uccuguagu 19

<210> SEQ ID NO 139
<211> LENGTH: 19
<212> TYPE: RNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: synthetic oligonucleotide

<400> SEQUENCE: 139

gagccgaagu cacagaaga 19

<210> SEQ ID NO 140
<211> LENGTH: 19
<212> TYPE: RNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: synthetic oligonucleotide

<400> SEQUENCE: 140

ggagccgaag ucacagaag 19

<210> SEQ ID NO 141
<211> LENGTH: 19
<212> TYPE: RNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: synthetic oligonucleotide

<400> SEQUENCE: 141

caaggccuga ccaugcaca 19

<210> SEQ ID NO 142
<211> LENGTH: 19

<212> TYPE: RNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: synthetic oligonucleotide

<400> SEQUENCE: 142

agcucaaacu ugauaggcu 19

<210> SEQ ID NO 143
<211> LENGTH: 19
<212> TYPE: RNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: synthetic oligonucleotide

<400> SEQUENCE: 143

cugcaguucu ggccgacgg 19

<210> SEQ ID NO 144
<211> LENGTH: 19
<212> TYPE: RNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: synthetic oligonucleotide

<400> SEQUENCE: 144

gguacauacu ccacagaau 19

<210> SEQ ID NO 145
<211> LENGTH: 19
<212> TYPE: RNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: synthetic oligonucleotide

<400> SEQUENCE: 145

cugcuucucu agccugcag 19

<210> SEQ ID NO 146
<211> LENGTH: 19
<212> TYPE: RNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: synthetic oligonucleotide

<400> SEQUENCE: 146

gcaaggccug accaugcac 19

<210> SEQ ID NO 147
<211> LENGTH: 19
<212> TYPE: RNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: synthetic oligonucleotide

<400> SEQUENCE: 147

cagaauuuag cucgguaug 19

<210> SEQ ID NO 148
<211> LENGTH: 19
<212> TYPE: RNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: synthetic oligonucleotide

<400> SEQUENCE: 148

ccaaacgugu cuuccaguc 19

<210> SEQ ID NO 149
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<220> FEATURE:
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<400> SEQUENCE: 149

cuucaugacc ucgccguca 19

<210> SEQ ID NO 150
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<212> TYPE: RNA
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<400> SEQUENCE: 150

gcuucgcaag gccugacca 19

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<212> TYPE: RNA
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<400> SEQUENCE: 151

ucagcuucgc aaggccuga 19

<210> SEQ ID NO 152
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<212> TYPE: RNA
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<220> FEATURE:
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<400> SEQUENCE: 152

gucuuccagu cgguaagcc 19

<210> SEQ ID NO 153
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<212> TYPE: RNA
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<400> SEQUENCE: 153

caaacuugau aggcuugga 19

<210> SEQ ID NO 154
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<212> TYPE: RNA
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aggucuugga acaggcgcu 19

<210> SEQ ID NO 155
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<212> TYPE: RNA
<213> ORGANISM: Artificial Sequence

<220> FEATURE:
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<400> SEQUENCE: 155

caggucagcu ucgcaaggc 19

<210> SEQ ID NO 156
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<212> TYPE: RNA
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<223> OTHER INFORMATION: synthetic oligonucleotide

<400> SEQUENCE: 156

gucagcuucg caaggccug 19

<210> SEQ ID NO 157
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<212> TYPE: RNA
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<400> SEQUENCE: 157

ggcguuguca uugguaacc 19

<210> SEQ ID NO 158
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<212> TYPE: RNA
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<220> FEATURE:
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<400> SEQUENCE: 158

cgugcacugg uacuugcag 19

<210> SEQ ID NO 159
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<223> OTHER INFORMATION: synthetic oligonucleotide

<400> SEQUENCE: 159

gucuuggaac aggcgcucc 19

<210> SEQ ID NO 160
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<212> TYPE: RNA
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<400> SEQUENCE: 160

ccaugucucc guacaucuu 19

<210> SEQ ID NO 161
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<400> SEQUENCE: 161

ggucagcuuc gcaaggccu 19

<210> SEQ ID NO 162
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<212> TYPE: RNA
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<400> SEQUENCE: 162

cagcuucgca aggccugac 19

<210> SEQ ID NO 163
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gccgaaguca cagaagagg 19

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<400> SEQUENCE: 164

cacagaauuu agcucggua 19

<210> SEQ ID NO 165
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<212> TYPE: RNA
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<400> SEQUENCE: 165

ccacagaauu uagcucggu 19

<210> SEQ ID NO 166
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<212> TYPE: RNA
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<220> FEATURE:
<223> OTHER INFORMATION: synthetic oligonucleotide

<400> SEQUENCE: 166

gccaaacgug ucuuccagu 19

<210> SEQ ID NO 167
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<212> TYPE: RNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: synthetic oligonucleotide

<400> SEQUENCE: 167

gccgaucuug cgguuggcc 19

<210> SEQ ID NO 168
<211> LENGTH: 19
<212> TYPE: RNA
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<400> SEQUENCE: 168

cucaaacuug auaggcuug 19

<210> SEQ ID NO 169
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<212> TYPE: RNA
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<400> SEQUENCE: 169

ccaggucagc uucgcaagg 19

<210> SEQ ID NO 170
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<400> SEQUENCE: 170

uuugacuaaa ugcaaagug 19

<210> SEQ ID NO 171
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<400> SEQUENCE: 171

uguuuuugua gccaaaucc 19

<210> SEQ ID NO 172
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<212> TYPE: RNA
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<400> SEQUENCE: 172

uguuuuugua gccaaaucc 19

<210> SEQ ID NO 173
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<212> TYPE: RNA
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<223> OTHER INFORMATION: synthetic oligonucleotide

<400> SEQUENCE: 173

uguuuuugua gccaaaucc 19

<210> SEQ ID NO 174
<211> LENGTH: 19
<212> TYPE: RNA
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<223> OTHER INFORMATION: synthetic oligonucleotide

<400> SEQUENCE: 174

aaaucguauu ugucaauca 19

<210> SEQ ID NO 175

<211> LENGTH: 19
<212> TYPE: RNA
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<400> SEQUENCE: 175

aaaucguauu ugucaauca 19

<210> SEQ ID NO 176
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<400> SEQUENCE: 176

gucaucacac ugaauaccaa u 21

<210> SEQ ID NO 177
<211> LENGTH: 21
<212> TYPE: RNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: synthetic oligonucleotide

<400> SEQUENCE: 177

gugaucagac ucaauacgaa u 21

<210> SEQ ID NO 178
<211> LENGTH: 13
<212> TYPE: RNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: synthetic oligonucleotide

<400> SEQUENCE: 178

cuguggaagu cua 13

<210> SEQ ID NO 179
<211> LENGTH: 13
<212> TYPE: RNA
<213> ORGANISM: Artificial Sequence
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<223> OTHER INFORMATION: synthetic oligonucleotide

<400> SEQUENCE: 179

cuguggaagu cua 13

<210> SEQ ID NO 180
<211> LENGTH: 13
<212> TYPE: RNA
<213> ORGANISM: Artificial Sequence
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<400> SEQUENCE: 180

cuguggaagu cua 13

<210> SEQ ID NO 181
<211> LENGTH: 13
<212> TYPE: RNA
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<400> SEQUENCE: 181

cuguggaagu cua 13

<210> SEQ ID NO 182
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<212> TYPE: RNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: synthetic oligonucleotide

<400> SEQUENCE: 182

cuguggaagu cua 13

<210> SEQ ID NO 183
<211> LENGTH: 13
<212> TYPE: RNA
<213> ORGANISM: Artificial Sequence
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<223> OTHER INFORMATION: synthetic oligonucleotide

<400> SEQUENCE: 183

cuguggaagu cua 13

<210> SEQ ID NO 184
<211> LENGTH: 13
<212> TYPE: RNA
<213> ORGANISM: Artificial Sequence
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<223> OTHER INFORMATION: synthetic oligonucleotide

<400> SEQUENCE: 184

cuguggaagu cua 13

<210> SEQ ID NO 185
<211> LENGTH: 13
<212> TYPE: RNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: synthetic oligonucleotide

<400> SEQUENCE: 185

cuguggaagu cua 13

<210> SEQ ID NO 186
<211> LENGTH: 13
<212> TYPE: RNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: synthetic oligonucleotide

<400> SEQUENCE: 186

cuguggaagu cua 13

<210> SEQ ID NO 187
<211> LENGTH: 13
<212> TYPE: RNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: synthetic oligonucleotide

<400> SEQUENCE: 187

cuguggaagu cua 13

<210> SEQ ID NO 188
<211> LENGTH: 21
<212> TYPE: RNA

<213> ORGANISM: Artificial Sequence
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<223> OTHER INFORMATION: synthetic oligonucleotide

<400> SEQUENCE: 188

gucaucacac ugaauaccaa u 21

<210> SEQ ID NO 189
<211> LENGTH: 21
<212> TYPE: RNA
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<223> OTHER INFORMATION: synthetic oligonucleotide

<400> SEQUENCE: 189

gugaucagac ucaauacgaa u 21

<210> SEQ ID NO 190
<211> LENGTH: 13
<212> TYPE: RNA
<213> ORGANISM: Artificial Sequence
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<223> OTHER INFORMATION: synthetic oligonucleotide

<400> SEQUENCE: 190

cuguggaagu cua 13

<210> SEQ ID NO 191
<211> LENGTH: 13
<212> TYPE: RNA
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<223> OTHER INFORMATION: synthetic oligonucleotide

<400> SEQUENCE: 191

cuguggaagu cua 13

<210> SEQ ID NO 192
<211> LENGTH: 13
<212> TYPE: RNA
<213> ORGANISM: Artificial Sequence
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<223> OTHER INFORMATION: synthetic oligonucleotide

<400> SEQUENCE: 192

cuguggaagu cua 13

<210> SEQ ID NO 193
<211> LENGTH: 13
<212> TYPE: RNA
<213> ORGANISM: Artificial Sequence
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<223> OTHER INFORMATION: synthetic oligonucleotide

<400> SEQUENCE: 193

cuguggaagu cua 13

<210> SEQ ID NO 194
<211> LENGTH: 13
<212> TYPE: RNA
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<220> FEATURE:
<223> OTHER INFORMATION: synthetic oligonucleotide

<400> SEQUENCE: 194

cuguggaagu cua 13

<210> SEQ ID NO 195
<211> LENGTH: 13
<212> TYPE: RNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: synthetic oligonucleotide

<400> SEQUENCE: 195

cuguggaagu cua 13

<210> SEQ ID NO 196
<211> LENGTH: 27
<212> TYPE: RNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: synthetic oligonucleotide

<400> SEQUENCE: 196

ucauagguaa ccucugguug aaaguga 27

<210> SEQ ID NO 197
<211> LENGTH: 27
<212> TYPE: RNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: synthetic oligonucleotide

<400> SEQUENCE: 197

cggcuacagg ugcuuaugaa gaaagua 27

<210> SEQ ID NO 198
<211> LENGTH: 21
<212> TYPE: RNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: synthetic oligonucleotide

<400> SEQUENCE: 198

gucaucacac ugaauaccaa u 21

<210> SEQ ID NO 199
<211> LENGTH: 21
<212> TYPE: RNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: synthetic oligonucleotide

<400> SEQUENCE: 199

gugaucagac ucaauacgaa u 21

<210> SEQ ID NO 200
<211> LENGTH: 13
<212> TYPE: RNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: synthetic oligonucleotide

<400> SEQUENCE: 200

cuguggaagu cua 13

<210> SEQ ID NO 201
<211> LENGTH: 21
<212> TYPE: RNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:

<223> OTHER INFORMATION: synthetic oligonucleotide

<400> SEQUENCE: 201

gucaucacac ugaauaccaa u 21

<210> SEQ ID NO 202
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<212> TYPE: RNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: synthetic oligonucleotide

<400> SEQUENCE: 202

gugaucagac ucaauacgaa u 21

<210> SEQ ID NO 203
<211> LENGTH: 13
<212> TYPE: RNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: synthetic oligonucleotide

<400> SEQUENCE: 203

uguaggaugu cua 13

<210> SEQ ID NO 204
<211> LENGTH: 13
<212> TYPE: RNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: synthetic oligonucleotide

<400> SEQUENCE: 204

cuguggaagu cua 13

<210> SEQ ID NO 205
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<212> TYPE: RNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: synthetic oligonucleotide

<400> SEQUENCE: 205

cuguggaagu cua 13

<210> SEQ ID NO 206
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<212> TYPE: RNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: synthetic oligonucleotide

<400> SEQUENCE: 206

acugaauacc aau 13

<210> SEQ ID NO 207
<211> LENGTH: 13
<212> TYPE: RNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: synthetic oligonucleotide

<400> SEQUENCE: 207

cuguggaagu cua 13

<210> SEQ ID NO 208
<211> LENGTH: 13
<212> TYPE: RNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: synthetic oligonucleotide

<400> SEQUENCE: 208

cuguggaagu cua 13

<210> SEQ ID NO 209
<211> LENGTH: 13
<212> TYPE: RNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: synthetic oligonucleotide

<400> SEQUENCE: 209

cuguggaagu cua 13

<210> SEQ ID NO 210
<211> LENGTH: 13
<212> TYPE: RNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: synthetic oligonucleotide

<400> SEQUENCE: 210

cuguggaagu cua 13

<210> SEQ ID NO 211
<211> LENGTH: 13
<212> TYPE: RNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: synthetic oligonucleotide

<400> SEQUENCE: 211

cuguggaagu cua 13

<210> SEQ ID NO 212
<211> LENGTH: 13
<212> TYPE: RNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: synthetic oligonucleotide

<400> SEQUENCE: 212

cuguggaagu cua 13

<210> SEQ ID NO 213
<211> LENGTH: 13
<212> TYPE: RNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: synthetic oligonucleotide

<400> SEQUENCE: 213

cuguggaagu cua 13

<210> SEQ ID NO 214
<211> LENGTH: 13
<212> TYPE: RNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: synthetic oligonucleotide

<400> SEQUENCE: 214

cuguggaagu cua 13

<210> SEQ ID NO 215
<211> LENGTH: 13
<212> TYPE: RNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: synthetic oligonucleotide

<400> SEQUENCE: 215

cuguggaagu cua 13

<210> SEQ ID NO 216
<211> LENGTH: 13
<212> TYPE: RNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: synthetic oligonucleotide

<400> SEQUENCE: 216

cuguggaagu cua 13

<210> SEQ ID NO 217
<211> LENGTH: 13
<212> TYPE: RNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: synthetic oligonucleotide

<400> SEQUENCE: 217

cuguggaagu cua 13

<210> SEQ ID NO 218
<211> LENGTH: 13
<212> TYPE: RNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: synthetic oligonucleotide

<400> SEQUENCE: 218

cuguggaagu cua 13

<210> SEQ ID NO 219
<211> LENGTH: 13
<212> TYPE: RNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: synthetic oligonucleotide

<400> SEQUENCE: 219

cuguggaagu cua 13

<210> SEQ ID NO 220
<211> LENGTH: 19
<212> TYPE: RNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: synthetic oligonucleotide

<400> SEQUENCE: 220

agaguucugu ggaagucua 19

<210> SEQ ID NO 221
<211> LENGTH: 19

<212> TYPE: RNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: synthetic oligonucleotide

<400> SEQUENCE: 221

agaguucugu ggaagucua 19

<210> SEQ ID NO 222
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<212> TYPE: RNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: synthetic oligonucleotide

<400> SEQUENCE: 222

auuuggcuac aaa 13

<210> SEQ ID NO 223
<211> LENGTH: 13
<212> TYPE: RNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: synthetic oligonucleotide

<400> SEQUENCE: 223

acaaauacga uuu 13

<210> SEQ ID NO 224
<211> LENGTH: 13
<212> TYPE: RNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: synthetic oligonucleotide

<400> SEQUENCE: 224

acaaauacga uuu 13

<210> SEQ ID NO 225
<211> LENGTH: 13
<212> TYPE: RNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: synthetic oligonucleotide

<400> SEQUENCE: 225

cuguggaagu cua 13

<210> SEQ ID NO 226
<211> LENGTH: 13
<212> TYPE: RNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: synthetic oligonucleotide

<400> SEQUENCE: 226

aaugaagaaa gua 13

<210> SEQ ID NO 227
<211> LENGTH: 13
<212> TYPE: RNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: synthetic oligonucleotide

<400> SEQUENCE: 227

agguggaaau gaa 13

<210> SEQ ID NO 228
<211> LENGTH: 13
<212> TYPE: RNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: synthetic oligonucleotide

<400> SEQUENCE: 228

agaaaguaca aag 13

<210> SEQ ID NO 229
<211> LENGTH: 13
<212> TYPE: RNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: synthetic oligonucleotide

<400> SEQUENCE: 229

gaaaguacaa aga 13

<210> SEQ ID NO 230
<211> LENGTH: 13
<212> TYPE: RNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: synthetic oligonucleotide

<400> SEQUENCE: 230

augugacugc uga 13

<210> SEQ ID NO 231
<211> LENGTH: 13
<212> TYPE: RNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: synthetic oligonucleotide

<400> SEQUENCE: 231

agacuugggc aau 13

<210> SEQ ID NO 232
<211> LENGTH: 13
<212> TYPE: RNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: synthetic oligonucleotide

<400> SEQUENCE: 232

auuucgagca gaa 13

<210> SEQ ID NO 233
<211> LENGTH: 13
<212> TYPE: RNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: synthetic oligonucleotide

<400> SEQUENCE: 233

aucuggagaa aca 13

<210> SEQ ID NO 234
<211> LENGTH: 13
<212> TYPE: RNA
<213> ORGANISM: Artificial Sequence

<220> FEATURE:
<223> OTHER INFORMATION: synthetic oligonucleotide

<400> SEQUENCE: 234

ucagaacaag aaa 13

<210> SEQ ID NO 235
<211> LENGTH: 13
<212> TYPE: RNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: synthetic oligonucleotide

<400> SEQUENCE: 235

gacucaucug cua 13

<210> SEQ ID NO 236
<211> LENGTH: 13
<212> TYPE: RNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: synthetic oligonucleotide

<400> SEQUENCE: 236

ggagaaacaa cau 13

<210> SEQ ID NO 237
<211> LENGTH: 13
<212> TYPE: RNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: synthetic oligonucleotide

<400> SEQUENCE: 237

agucccucaa aca 13

<210> SEQ ID NO 238
<211> LENGTH: 13
<212> TYPE: RNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: synthetic oligonucleotide

<400> SEQUENCE: 238

ggcuacaaaa aca 13

<210> SEQ ID NO 239
<211> LENGTH: 15
<212> TYPE: RNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: synthetic oligonucleotide

<400> SEQUENCE: 239

agaucuggag aaaca 15

<210> SEQ ID NO 240
<211> LENGTH: 15
<212> TYPE: RNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: synthetic oligonucleotide

<400> SEQUENCE: 240

uggacucauc ugcua 15

<210> SEQ ID NO 241
<211> LENGTH: 15
<212> TYPE: RNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: synthetic oligonucleotide

<400> SEQUENCE: 241

cuggagaaac aacau 15

<210> SEQ ID NO 242
<211> LENGTH: 15
<212> TYPE: RNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: synthetic oligonucleotide

<400> SEQUENCE: 242

agagucccuc aaaca 15

<210> SEQ ID NO 243
<211> LENGTH: 13
<212> TYPE: RNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: synthetic oligonucleotide

<400> SEQUENCE: 243

acugaauacc aau 13

<210> SEQ ID NO 244
<211> LENGTH: 15
<212> TYPE: RNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: synthetic oligonucleotide

<400> SEQUENCE: 244

acacugaaua ccaau 15

<210> SEQ ID NO 245
<211> LENGTH: 13
<212> TYPE: RNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: synthetic oligonucleotide

<400> SEQUENCE: 245

aaugaagaaa gua 13

<210> SEQ ID NO 246
<211> LENGTH: 13
<212> TYPE: RNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: synthetic oligonucleotide

<400> SEQUENCE: 246

agguggaaau gaa 13

<210> SEQ ID NO 247
<211> LENGTH: 13
<212> TYPE: RNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: synthetic oligonucleotide

<400> SEQUENCE: 247

agaaaguaca aag 13

<210> SEQ ID NO 248
<211> LENGTH: 13
<212> TYPE: RNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: synthetic oligonucleotide

<400> SEQUENCE: 248

gaaaguacaa aga 13

<210> SEQ ID NO 249
<211> LENGTH: 13
<212> TYPE: RNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: synthetic oligonucleotide

<400> SEQUENCE: 249

augugacugc uga 13

<210> SEQ ID NO 250
<211> LENGTH: 13
<212> TYPE: RNA
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agacuugggc aau 13

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auuucgagca gaa 13

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acaaauacga uuu 13

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acaaauacga uuu 13

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agaguucugu ggaagucua 19

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acaggaagau gua 13

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gaguggagcg ccu 13

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cgacuggaag aca 13

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ggagcgccug uuc 13

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gccauuacaa cug 13

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gagcuuucug gcu 13

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aguggagcgc cug 13

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uggagcgccu guu 13

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guuugagcuu ucu 13

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ugccauuaca acu 13

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acuggaagac acg 13

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aacugccugg ucc 13

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agaccugugc cug 13

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cagaguggag cgc 13

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ccugguccag acc 13

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ccauuacaac ugu 13

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cugccauuac aac 13

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auuacaacug ucc 13

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cauuacaacu guc 13

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agaguggagc gcc 13

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accgacugga aga 13

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auguacggag aca 13

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gccuugcgaa gcu 13

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gcugcgagga gug 13

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gccuaucaag uuu 13

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aauucugugg agu 13

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uguacggaga cau 13

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agccuaucaa guu 13

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caaguuugag cuu 13

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cuguggagua ugu 13

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aaauucugug gag 13

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uuucaguagc aca 13

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caaugacauc uuu 13

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aguaccagug cac 13

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ggaagacacg uuu 13

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cuaucaaguu uga 13

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agcuaaauuc ugu 13

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agguagaaug uaa 13

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agcugaucag uuu 13

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uucugcucag aua 13

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uuaucuaagu uaa 13

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uauacgagua aua 13

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gacuggacag cuu 13

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auggccuuua uua 13

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auaccgagcu aaa 13

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uuguugagag ugu 13

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acauaccgag cua 13

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agcagaaagg uua 13

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aguuguuccu uaa 13

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auuugaagug uaa 13

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aagcugaccu gga 13

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ggucaugaag aag 13

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auggucaggc cuu 13

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gaagacacgu uug 13

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aggccuugcg aag 13

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uaccgacugg aag 13

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accgcaagau cgg 13

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<400> SEQUENCE: 312

caggccuugc gaa 13

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<400> SEQUENCE: 313

cgagcuaaau ucu 13

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ucuguggagu aug 13

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cggagacaug gca 13

<210> SEQ ID NO 316
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augacaacgc cuc 13

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gaggucauga aga 13

<210> SEQ ID NO 318
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uaaauucugu gga 13

<210> SEQ ID NO 319
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uggaagacac guu 13

<210> SEQ ID NO 320
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<400> SEQUENCE: 320

aagauguacg gag 13

<210> SEQ ID NO 321
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aaugacaacg ccu 13

<210> SEQ ID NO 322
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ggcgagguca uga 13

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<400> SEQUENCE: 323

gacacguuug gcc 13

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<400> SEQUENCE: 324

acggagacau ggc 13

<210> SEQ ID NO 325
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ucaggccuug cga 13

<210> SEQ ID NO 326
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gcgaagcuga ccu 13

<210> SEQ ID NO 327
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ggaagaugua cgg 13

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gugacuucgg cuc 13

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ugacuucggc ucc 13

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<400> SEQUENCE: 330

uggucaggcc uug 13

<210> SEQ ID NO 331
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<400> SEQUENCE: 331

ucaaguuuga gcu 13

<210> SEQ ID NO 332
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<400> SEQUENCE: 332

gccagaacug cag 13

<210> SEQ ID NO 333

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<400> SEQUENCE: 333

uggaguaugu acc 13

<210> SEQ ID NO 334
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gcuagagaag cag 13

<210> SEQ ID NO 335
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<400> SEQUENCE: 335

ggucaggccu ugc 13

<210> SEQ ID NO 336
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<400> SEQUENCE: 336

gagcuaaauu cug 13

<210> SEQ ID NO 337
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<400> SEQUENCE: 337

aagacacguu ugg 13

<210> SEQ ID NO 338
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cgaggucaug aag 13

<210> SEQ ID NO 339
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<400> SEQUENCE: 339

ggccuugcga agc 13

<210> SEQ ID NO 340
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<400> SEQUENCE: 340

cuugcgaagc uga 13

<210> SEQ ID NO 341
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<400> SEQUENCE: 341

ccgacuggaa gac 13

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ccuaucaagu uug 13

<210> SEQ ID NO 343
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uguuccaaga ccu 13

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cgaagcugac cug 13

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uugcgaagcu gac 13

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<400> SEQUENCE: 346

caaugacaac gcc 13

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guaccagugc acg 13

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ccuguuccaa gac 13

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uacggagaca ugg 13

<210> SEQ ID NO 350
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<400> SEQUENCE: 350

ugcgaagcug acc 13

<210> SEQ ID NO 351
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ccuugcgaag cug 13

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cugugacuuc ggc 13

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gcuaaauucu gug 13

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cuaaauucug ugg 13

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agacacguuu ggc 13

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ccgcaagauc ggc 13

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uaucaaguuu gag 13

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gaagcugacc ugg 13

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cucaugaauu aga 13

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cugaggucaa uua 13

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gaggucaauu aaa 13

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ucugagguca auu 13

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ugaggucaau uaa 13

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uucugagguc aau 13

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gucagcugga uga 13

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uucugaugaa ucu 13

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uggacugagg uca 13

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gagucucacc auu 13

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gacugagguc aaa 13

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ucacagccau gaa 13

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agucucacca uuc 13

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aagcggaaag cca 13

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agcggaaagc caa 13

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accacaugga uga 13

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gccaugacca cau 13

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aagccaugac cac 13

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gcggaaagcc aau 13

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aaauuucgua uuu 13

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auuucguauu ucu 13

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aaagccauga cca 13

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acauggauga uau 13

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gaaauuucgu auu 13

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gcgccuucug auu 13

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auuucucaug aau 13

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cucucaugaa uag 13

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aaguccaacg aaa 13

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augaugagag caa 13

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gcgaggaguu gaa 13

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ugauugauag uca 13

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agauagugca ucu 13

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auguguaucu auu 13

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uucuauagaa gaa 13

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uuguccagca auu 13

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acauggaaag cga 13

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gcaguccaga uua 13

<210> SEQ ID NO 396
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ugguugaaug ugu 13

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uuaugaaacg agu 13

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caguccagau uau 13

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auauaagcgg aaa 13

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uaccaguuaa aca 13

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uguucauucu aua 13

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ccgaccaagg aaa 13

<210> SEQ ID NO 403
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gaauggugca uac 13

<210> SEQ ID NO 404
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<400> SEQUENCE: 404

auaugauggc cga 13

<210> SEQ ID NO 405
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<400> SEQUENCE: 405

agcaguccag auu 13

<210> SEQ ID NO 406
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<400> SEQUENCE: 406

gcauuuaguc aaa 13

<210> SEQ ID NO 407
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agcauuccga ugu 13

<210> SEQ ID NO 408
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uagucaggaa cuu 13

<210> SEQ ID NO 409
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ugcauuuagu caa 13

<210> SEQ ID NO 410
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gucugaugag ucu 13

<210> SEQ ID NO 411
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uagacacaua uga 13

<210> SEQ ID NO 412

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<400> SEQUENCE: 412

cagacgagga cau 13

<210> SEQ ID NO 413
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cagccgugaa uuc 13

<210> SEQ ID NO 414
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<400> SEQUENCE: 414

agucuggaaa uaa 13

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<400> SEQUENCE: 415

aguuuguggc uuc 13

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aguccaacga aag 13

<210> SEQ ID NO 417
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<212> TYPE: RNA
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<400> SEQUENCE: 417

aaguuucgca gac 13

<210> SEQ ID NO 418
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<212> TYPE: RNA
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<400> SEQUENCE: 418

agcaaugagc auu 13

<210> SEQ ID NO 419
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uuagauagug cau 13

<210> SEQ ID NO 420
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<212> TYPE: RNA
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uggugcauac aag 13

<210> SEQ ID NO 421
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<400> SEQUENCE: 421

augaaacgag uca 13

<210> SEQ ID NO 422
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ccagagugcu gaa 13

<210> SEQ ID NO 423
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<400> SEQUENCE: 423

cagccaugaa uuu 13

<210> SEQ ID NO 424
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auugguugaa ugu 13

<210> SEQ ID NO 425
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<213> ORGANISM: Artificial Sequence
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<400> SEQUENCE: 425

gguugaaugu gua 13

<210> SEQ ID NO 426
<211> LENGTH: 13
<212> TYPE: RNA
<213> ORGANISM: Artificial Sequence
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<400> SEQUENCE: 426

ggaaauaacu aau 13

<210> SEQ ID NO 427
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<212> TYPE: RNA
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<400> SEQUENCE: 427

ucaugaauag aaa 13

<210> SEQ ID NO 428
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<400> SEQUENCE: 428

gccagcaacc gaa 13

<210> SEQ ID NO 429
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caccucacac aug 13

<210> SEQ ID NO 430
<211> LENGTH: 13
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<400> SEQUENCE: 430

aguugaaugg ugc 13

<210> SEQ ID NO 431
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<212> TYPE: RNA
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<400> SEQUENCE: 431

agucagcugg aug 13

<210> SEQ ID NO 432
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<212> TYPE: RNA
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<400> SEQUENCE: 432

uauaagcgga aag 13

<210> SEQ ID NO 433
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<212> TYPE: RNA
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uuccgaugug auu 13

<210> SEQ ID NO 434
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<212> TYPE: RNA
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<400> SEQUENCE: 434

auaacuaaug ugu 13

<210> SEQ ID NO 435
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<212> TYPE: RNA
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<400> SEQUENCE: 435

ucauucuaua gaa 13

<210> SEQ ID NO 436
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<212> TYPE: RNA
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<400> SEQUENCE: 436

aacuaucacu gua 13

<210> SEQ ID NO 437
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<212> TYPE: RNA
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<400> SEQUENCE: 437

gucaauugcu uau 13

<210> SEQ ID NO 438
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<223> OTHER INFORMATION: synthetic oligonucleotide

<400> SEQUENCE: 438

agcaauuaau aaa 13

<210> SEQ ID NO 439
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acgacucuga uga 13

<210> SEQ ID NO 440
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<400> SEQUENCE: 440

uagugugguu uau 13

<210> SEQ ID NO 441
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<400> SEQUENCE: 441

aagccaauga uga 13

<210> SEQ ID NO 442
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auagucagga acu 13

<210> SEQ ID NO 443
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<400> SEQUENCE: 443

agucagccgu gaa 13

<210> SEQ ID NO 444
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acuaccauga gaa 13

<210> SEQ ID NO 445
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<400> SEQUENCE: 445

aaacaggcug auu 13

<210> SEQ ID NO 446
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<400> SEQUENCE: 446

gagugcugaa acc 13

<210> SEQ ID NO 447
<211> LENGTH: 13
<212> TYPE: RNA
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ugagcauucc gau 13

<210> SEQ ID NO 448
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<400> SEQUENCE: 448

aauuccacag cca 13

<210> SEQ ID NO 449
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ugucaauugc uua 13

<210> SEQ ID NO 450
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accaugagaa uug 13

<210> SEQ ID NO 451
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<400> SEQUENCE: 451

ccaacgaaag cca 13

<210> SEQ ID NO 452
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<400> SEQUENCE: 452

cuggucacug auu 13

<210> SEQ ID NO 453
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<400> SEQUENCE: 453

ugguuuaugg acu 13

<210> SEQ ID NO 454
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<212> TYPE: RNA
<213> ORGANISM: Artificial Sequence
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<400> SEQUENCE: 454

gaccagagug cug 13

<210> SEQ ID NO 455
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gaugugauug aua 13

<210> SEQ ID NO 456
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gucagccgug aau 13

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aauguguauc uau 13

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ccugguccag acc 13

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uguacggaga cau 13

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aaauucugug gag 13

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uuguugagag ugu 13

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gaagacacgu uug 13

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gaggucauga aga 13

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uaaauucugu gga 13

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uggaagacac guu 13

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aaugacaacg ccu 13

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ggcgagguca uga 13

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acggagacau ggc 13

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ggaagaugua cgg 13

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gugacuucgg cuc 13

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ugacuucggc ucc 13

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uggucaggcc uug 13

<210> SEQ ID NO 561
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<223> OTHER INFORMATION: synthetic oligonucleotide

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ucaaguuuga gcu 13

<210> SEQ ID NO 562
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<212> TYPE: RNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
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<400> SEQUENCE: 562

gccagaacug cag 13

<210> SEQ ID NO 563
<211> LENGTH: 13
<212> TYPE: RNA
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<400> SEQUENCE: 563

uggaguaugu acc 13

<210> SEQ ID NO 564
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<212> TYPE: RNA
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<400> SEQUENCE: 564

gcuagagaag cag 13

<210> SEQ ID NO 565
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<212> TYPE: RNA
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<400> SEQUENCE: 565

ggucaggccu ugc 13

<210> SEQ ID NO 566
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<400> SEQUENCE: 566

gagcuaaauu cug 13

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<212> TYPE: RNA
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aagacacguu ugg 13

<210> SEQ ID NO 568
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cgaggucaug aag 13

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ggccuugcga agc 13

<210> SEQ ID NO 570

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<212> TYPE: RNA
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cuugcgaagc uga 13

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<400> SEQUENCE: 571

ccgacuggaa gac 13

<210> SEQ ID NO 572
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<212> TYPE: RNA
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<400> SEQUENCE: 572

ccuaucaagu uug 13

<210> SEQ ID NO 573
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<212> TYPE: RNA
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uguuccaaga ccu 13

<210> SEQ ID NO 574
<211> LENGTH: 13
<212> TYPE: RNA
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<400> SEQUENCE: 574

cgaagcugac cug 13

<210> SEQ ID NO 575
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uugcgaagcu gac 13

<210> SEQ ID NO 576
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<212> TYPE: RNA
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caaugacaac gcc 13

<210> SEQ ID NO 577
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<400> SEQUENCE: 577

guaccagugc acg 13

<210> SEQ ID NO 578
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<400> SEQUENCE: 578

ccuguuccaa gac 13

<210> SEQ ID NO 579
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<212> TYPE: RNA
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uacggagaca ugg 13

<210> SEQ ID NO 580
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<212> TYPE: RNA
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<400> SEQUENCE: 580

ugcgaagcug acc 13

<210> SEQ ID NO 581
<211> LENGTH: 13
<212> TYPE: RNA
<213> ORGANISM: Artificial Sequence
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<400> SEQUENCE: 581

ccuugcgaag cug 13

<210> SEQ ID NO 582
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<212> TYPE: RNA
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cugugacuuc ggc 13

<210> SEQ ID NO 583
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<212> TYPE: RNA

<213> ORGANISM: Artificial Sequence
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<400> SEQUENCE: 583

gcuaaauucu gug 13

<210> SEQ ID NO 584
<211> LENGTH: 13
<212> TYPE: RNA
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cuaaauucug ugg 13

<210> SEQ ID NO 585
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<212> TYPE: RNA
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<400> SEQUENCE: 585

agacacguuu ggc 13

<210> SEQ ID NO 586
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<212> TYPE: RNA
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<400> SEQUENCE: 586

ccgcaagauc ggc 13

<210> SEQ ID NO 587
<211> LENGTH: 13
<212> TYPE: RNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: synthetic oligonucleotide

<400> SEQUENCE: 587

uaucaaguuu gag 13

<210> SEQ ID NO 588
<211> LENGTH: 13
<212> TYPE: RNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: synthetic oligonucleotide

<400> SEQUENCE: 588

gaagcugacc ugg 13

<210> SEQ ID NO 589
<211> LENGTH: 13
<212> TYPE: RNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: synthetic oligonucleotide

<400> SEQUENCE: 589

gcauuuaguc aaa 13

<210> SEQ ID NO 590
<211> LENGTH: 13
<212> TYPE: RNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: synthetic oligonucleotide

<400> SEQUENCE: 590

ggcuacaaaa aca 13

<210> SEQ ID NO 591
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<212> TYPE: RNA
<213> ORGANISM: Artificial Sequence
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<400> SEQUENCE: 591

uuggcuacaa aaaca 15

<210> SEQ ID NO 592
<211> LENGTH: 17
<212> TYPE: RNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: synthetic oligonucleotide

<400> SEQUENCE: 592

auuuggcuac aaaaaca 17

<210> SEQ ID NO 593
<211> LENGTH: 13
<212> TYPE: RNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: synthetic oligonucleotide

<400> SEQUENCE: 593

acaaauacga uuu 13

<210> SEQ ID NO 594
<211> LENGTH: 13
<212> TYPE: RNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: synthetic oligonucleotide

<400> SEQUENCE: 594

acaaauacga uuu 13

<210> SEQ ID NO 595
<211> LENGTH: 25
<212> TYPE: RNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: synthetic oligonucleotide

<400> SEQUENCE: 595

cuuugaagag uucuguggaa gucua 25

<210> SEQ ID NO 596
<211> LENGTH: 23
<212> TYPE: RNA
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<220> FEATURE:

<223> OTHER INFORMATION: synthetic oligonucleotide

<400> SEQUENCE: 596

acaaacacca uugucacacu cca 23

<210> SEQ ID NO 597
<211> LENGTH: 19
<212> TYPE: RNA
<213> ORGANISM: Artificial sequence
<220> FEATURE:
<223> OTHER INFORMATION: synthetic oligonucleotide

<400> SEQUENCE: 597

uagacuucca cagaacucu 19

<210> SEQ ID NO 598
<211> LENGTH: 13
<212> TYPE: RNA
<213> ORGANISM: Artificial sequence
<220> FEATURE:
<223> OTHER INFORMATION: synthetic oligonucleotide

<400> SEQUENCE: 598

cuguggaagu cua 13

<210> SEQ ID NO 599
<211> LENGTH: 32
<212> TYPE: RNA
<213> ORGANISM: Artificial sequence
<220> FEATURE:
<223> OTHER INFORMATION: synthetic oligonuclotide

<400> SEQUENCE: 599

uagacuucca cagaacucug acaccuucag au 32

<210> SEQ ID NO 600
<211> LENGTH: 13
<212> TYPE: RNA
<213> ORGANISM: Artificial sequence
<220> FEATURE:
<223> OTHER INFORMATION: synthetic oligonucleotide

<400> SEQUENCE: 600

uagacuucca cag 13

<210> SEQ ID NO 601
<211> LENGTH: 13
<212> TYPE: RNA
<213> ORGANISM: Artificial sequence
<220> FEATURE:
<223> OTHER INFORMATION: synthetic oligonucleotide

<400> SEQUENCE: 601

cuguggaagu cua 13

<210> SEQ ID NO 602
<211> LENGTH: 31
<212> TYPE: RNA
<213> ORGANISM: Artificial sequence
<220> FEATURE:
<223> OTHER INFORMATION: synthetic oligonucleotide

<400> SEQUENCE: 602

uagacuucca cagaacucuu guggaagucu a 31

<210> SEQ ID NO 603
<211> LENGTH: 31
<212> TYPE: RNA
<213> ORGANISM: Artificial sequence
<220> FEATURE:
<223> OTHER INFORMATION: synthetic oligonucleotide

<400> SEQUENCE: 603

uagacuucca cagaacucuu guggaagucu a 31

<210> SEQ ID NO 604
<211> LENGTH: 25
<212> TYPE: RNA
<213> ORGANISM: Artificial sequence
<220> FEATURE:
<223> OTHER INFORMATION: synthetic oligonucleotide

<400> SEQUENCE: 604

cuuugaagag uucuguggaa gucua 25

<210> SEQ ID NO 605
<211> LENGTH: 25
<212> TYPE: RNA
<213> ORGANISM: Artificial sequence
<220> FEATURE:
<223> OTHER INFORMATION: synthetic oligonucleotide

<400> SEQUENCE: 605

uagacuucca cagaacucuu caaag 25

<210> SEQ ID NO 606
<211> LENGTH: 31
<212> TYPE: RNA
<213> ORGANISM: Artificial sequence
<220> FEATURE:
<223> OTHER INFORMATION: synthetic oligonucleotide

<400> SEQUENCE: 606

uagacuucca cagaacuucu guggaagucu a 31

<210> SEQ ID NO 607
<211> LENGTH: 31
<212> TYPE: RNA
<213> ORGANISM: Artificial sequence
<220> FEATURE:
<223> OTHER INFORMATION: synthetic oligonucleotide

<400> SEQUENCE: 607

uagacuucca cagaacuucu guggaagucu a 31

<210> SEQ ID NO 608
<211> LENGTH: 13
<212> TYPE: RNA
<213> ORGANISM: Artificial sequence
<220> FEATURE:
<223> OTHER INFORMATION: synthetoc oligonucleotide

<400> SEQUENCE: 608

uacuuucuuc auu 13

<210> SEQ ID NO 609
<211> LENGTH: 13
<212> TYPE: RNA
<213> ORGANISM: Artificial sequence
<220> FEATURE:
<223> OTHER INFORMATION: synthetic oligonucleotide

<400> SEQUENCE: 609

aaugaagaaa gua 13

<210> SEQ ID NO 610
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<212> TYPE: RNA
<213> ORGANISM: Artificial sequence
<220> FEATURE:
<223> OTHER INFORMATION: synthetic oligonucleotide

<400> SEQUENCE: 610

uacuuucuuc auuuccacca augaagaaag ua 32

<210> SEQ ID NO 611
<211> LENGTH: 32
<212> TYPE: RNA
<213> ORGANISM: Artificial sequence
<220> FEATURE:
<223> OTHER INFORMATION: synthetic oligonucleotide

<400> SEQUENCE: 611

uacuuucuuc auuuccacca augaagaaag ua 32

<210> SEQ ID NO 612
<211> LENGTH: 19
<212> TYPE: RNA
<213> ORGANISM: Artificial sequence
<220> FEATURE:
<223> OTHER INFORMATION: synthetic oligonucleotide

<400> SEQUENCE: 612

uacuuucuuc auuuccacc 19

<210> SEQ ID NO 613
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<212> TYPE: RNA
<213> ORGANISM: Artificial sequence
<220> FEATURE:
<223> OTHER INFORMATION: synthetic oligonucleotide

<400> SEQUENCE: 613

aaugaagaaa gua 13

<210> SEQ ID NO 614
<211> LENGTH: 25
<212> TYPE: RNA
<213> ORGANISM: Artificial sequence
<220> FEATURE:
<223> OTHER INFORMATION: synthetic oligonucleotide

<400> SEQUENCE: 614

uacuuucuuc auuuccaccu uugcc 25

<210> SEQ ID NO 615
<211> LENGTH: 25
<212> TYPE: RNA
<213> ORGANISM: Artificial sequence
<220> FEATURE:
<223> OTHER INFORMATION: synthetic oligonucleotide

<400> SEQUENCE: 615

ggcaaaggug gaaaugaaga aagua 25

<210> SEQ ID NO 616
<211> LENGTH: 19

<212> TYPE: RNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: synthetic oligonucleotide

<400> SEQUENCE: 616

ucuaauucau gagaaauac 19

<210> SEQ ID NO 617
<211> LENGTH: 19
<212> TYPE: RNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: synthetic oligonucleotide

<400> SEQUENCE: 617

uaauugaccu cagaagaug 19

<210> SEQ ID NO 618
<211> LENGTH: 19
<212> TYPE: RNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: synthetic oligonucleotide

<400> SEQUENCE: 618

uuuaauugac cucagaaga 19

<210> SEQ ID NO 619
<211> LENGTH: 19
<212> TYPE: RNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: synthetic oligonucleotide

<400> SEQUENCE: 619

aauugaccuc agaagaugc 19

<210> SEQ ID NO 620
<211> LENGTH: 19
<212> TYPE: RNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: synthetic oligonucleotide

<400> SEQUENCE: 620

uuaauugacc ucagaagau 19

<210> SEQ ID NO 621
<211> LENGTH: 19
<212> TYPE: RNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: synthetic oligonucleotide

<400> SEQUENCE: 621

auugaccuca gaagaugca 19

<210> SEQ ID NO 622
<211> LENGTH: 19
<212> TYPE: RNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: synthetic oligonucleotide

<400> SEQUENCE: 622

ucauccagcu gacucguuu 19

<210> SEQ ID NO 623
<211> LENGTH: 19
<212> TYPE: RNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: synthetic oligonucleotide

<400> SEQUENCE: 623

agauucauca gaaugguga 19

<210> SEQ ID NO 624
<211> LENGTH: 19
<212> TYPE: RNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: synthetic oligonucleotide

<400> SEQUENCE: 624

ugaccucagu ccauaaacc 19

<210> SEQ ID NO 625
<211> LENGTH: 19
<212> TYPE: RNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: synthetic oligonucleotide

<400> SEQUENCE: 625

aauggugaga cucaucaga 19

<210> SEQ ID NO 626
<211> LENGTH: 19
<212> TYPE: RNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: synthetic oligonucleotide

<400> SEQUENCE: 626

uuugaccuca guccauaaa 19

<210> SEQ ID NO 627
<211> LENGTH: 19
<212> TYPE: RNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: synthetic oligonucleotide

<400> SEQUENCE: 627

uucauggcug ugaaauuca 19

<210> SEQ ID NO 628
<211> LENGTH: 19
<212> TYPE: RNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: synthetic oligonucleotide

<400> SEQUENCE: 628

gaauggugag acucaucag 19

<210> SEQ ID NO 629
<211> LENGTH: 19
<212> TYPE: RNA
<213> ORGANISM: Artificial Sequence

<220> FEATURE:
<223> OTHER INFORMATION: synthetic oligonucleotide

<400> SEQUENCE: 629

uggcuuuccg cuuauauaa 19

<210> SEQ ID NO 630
<211> LENGTH: 19
<212> TYPE: RNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: synthetic oligonucleotide

<400> SEQUENCE: 630

uuggcuuucc gcuuauaua 19

<210> SEQ ID NO 631
<211> LENGTH: 19
<212> TYPE: RNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: synthetic oligonucleotide

<400> SEQUENCE: 631

ucauccaugu ggucauggc 19

<210> SEQ ID NO 632
<211> LENGTH: 19
<212> TYPE: RNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: synthetic oligonucleotide

<400> SEQUENCE: 632

auguggucau ggcuuucgu 19

<210> SEQ ID NO 633
<211> LENGTH: 19
<212> TYPE: RNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: synthetic oligonucleotide

<400> SEQUENCE: 633

guggucaugg cuuucguug 19

<210> SEQ ID NO 634
<211> LENGTH: 19
<212> TYPE: RNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: synthetic oligonucleotide

<400> SEQUENCE: 634

auuggcuuuc cgcuuauau 19

<210> SEQ ID NO 635
<211> LENGTH: 19
<212> TYPE: RNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: synthetic oligonucleotide

<400> SEQUENCE: 635

aaauacgaaa uuucaggug 19

<210> SEQ ID NO 636
<211> LENGTH: 19
<212> TYPE: RNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: synthetic oligonucleotide

<400> SEQUENCE: 636

agaaauacga aauuucagg 19

<210> SEQ ID NO 637
<211> LENGTH: 19
<212> TYPE: RNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: synthetic oligonucleotide

<400> SEQUENCE: 637

uggucauggc uuucguugg 19

<210> SEQ ID NO 638
<211> LENGTH: 19
<212> TYPE: RNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: synthetic oligonucleotide

<400> SEQUENCE: 638

auaucaucca uguggucau 19

<210> SEQ ID NO 639
<211> LENGTH: 19
<212> TYPE: RNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: synthetic oligonucleotide

<400> SEQUENCE: 639

aauacgaaau uucaggugu 19

<210> SEQ ID NO 640
<211> LENGTH: 19
<212> TYPE: RNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: synthetic oligonucleotide

<400> SEQUENCE: 640

aaucagaagg cgcguucag 19

<210> SEQ ID NO 641
<211> LENGTH: 19
<212> TYPE: RNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: synthetic oligonucleotide

<400> SEQUENCE: 641

auucaugaga aauacgaaa 19

<210> SEQ ID NO 642
<211> LENGTH: 19
<212> TYPE: RNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: synthetic oligonucleotide

<400> SEQUENCE: 642

cuauucauga gagaauaac 19

<210> SEQ ID NO 643
<211> LENGTH: 19
<212> TYPE: RNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: synthetic oligonucleotide

<400> SEQUENCE: 643

uuucguugga cuuacuugg 19

<210> SEQ ID NO 644
<211> LENGTH: 19
<212> TYPE: RNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: synthetic oligonucleotide

<400> SEQUENCE: 644

uugcucucau cauuggcuu 19

<210> SEQ ID NO 645
<211> LENGTH: 19
<212> TYPE: RNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: synthetic oligonucleotide

<400> SEQUENCE: 645

uucaacuccu cgcuuucca 19

<210> SEQ ID NO 646
<211> LENGTH: 19
<212> TYPE: RNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: synthetic oligonucleotide

<400> SEQUENCE: 646

ugacuaucaa ucacaucgg 19

<210> SEQ ID NO 647
<211> LENGTH: 19
<212> TYPE: RNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: synthetic oligonucleotide

<400> SEQUENCE: 647

agaugcacua ucuaauuca 19

<210> SEQ ID NO 648
<211> LENGTH: 19
<212> TYPE: RNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: synthetic oligonucleotide

<400> SEQUENCE: 648

aauagauaca cauucaacc 19

<210> SEQ ID NO 649

<211> LENGTH: 19
<212> TYPE: RNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: synthetic oligonucleotide

<400> SEQUENCE: 649

uucuucuaua gaaugaaca 19

<210> SEQ ID NO 650
<211> LENGTH: 19
<212> TYPE: RNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: synthetic oligonucleotide

<400> SEQUENCE: 650

aauugcugga caaccgugg 19

<210> SEQ ID NO 651
<211> LENGTH: 19
<212> TYPE: RNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: synthetic oligonucleotide

<400> SEQUENCE: 651

ucgcuuucca ugugugagg 19

<210> SEQ ID NO 652
<211> LENGTH: 19
<212> TYPE: RNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: synthetic oligonucleotide

<400> SEQUENCE: 652

uaaucuggac ugcuugugg 19

<210> SEQ ID NO 653
<211> LENGTH: 19
<212> TYPE: RNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: synthetic oligonucleotide

<400> SEQUENCE: 653

acacauucaa ccaauaaac 19

<210> SEQ ID NO 654
<211> LENGTH: 19
<212> TYPE: RNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: synthetic oligonucleotide

<400> SEQUENCE: 654

acucguuuca uaacugucc 19

<210> SEQ ID NO 655
<211> LENGTH: 19
<212> TYPE: RNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: synthetic oligonucleotide

<400> SEQUENCE: 655

auaaaucugga cugcuugug 19

<210> SEQ ID NO 656
<211> LENGTH: 19
<212> TYPE: RNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: synthetic oligonucleotide

<400> SEQUENCE: 656

uuuccgcuua uauaaucug 19

<210> SEQ ID NO 657
<211> LENGTH: 19
<212> TYPE: RNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: synthetic oligonucleotide

<400> SEQUENCE: 657

uguuuaacug guauggcac 19

<210> SEQ ID NO 658
<211> LENGTH: 19
<212> TYPE: RNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: synthetic oligonucleotide

<400> SEQUENCE: 658

uauagaauga acauagaca 19

<210> SEQ ID NO 659
<211> LENGTH: 19
<212> TYPE: RNA
<213> ORGANISM: Artificial Sequence
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guaugcacca uucaacucc 19

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ucggccauca uaugugucu 19

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aaucuggacu gcuuguggc 19

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acaucggaau gcucauugc 19

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agacucauca gacuggugа 19

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cuuucguugg acuuacuug 19

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ugacucguuu cauaacugu 19

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acauucaacc aauaaacug 19

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uuucuauuca ugagagaau 19

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uucgguugcu ggcaggucc 19

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gcaccauuca acuccucgc 19

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cauccagcug acucguuuc 19

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cuuuccgcuu auauaaucu 19

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aaucacaucg gaaugcuca 19

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acacauuagu uauuuccag 19

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uucuauagaa ugaacauag 19

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auaagcaauu gacaccacc 19

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uuuauuaauu gcuggacaa 19

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ucaucagagu cguucgagu 19

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auaaaccaca cuaucaccu 19

<210> SEQ ID NO 697
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ucaucauugg cuuuccgcu 19

<210> SEQ ID NO 698
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aguuccugac uaucaauca 19

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uucacggcug acuuuggaa 19

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uucucauggu agugaguuu 19

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aaucagccug uuuaacugg 19

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gguuucagca cucugguca 19

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aucggaaugc ucauugcuc 19

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uggcugugga auucacggc 19

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caauucucau gguagugag 19

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<400> SEQUENCE: 707

uggcuuucgu uggacuuac 19

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<400> SEQUENCE: 708

aaucagugac caguucauc                                            19


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aguccauaaa ccacacuau                                            19


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cagcacucug gucauccag                                            19


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uaucaaucac aucggaaug                                            19


<210> SEQ ID NO 712
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auucacggcu gacuuugga                                            19


<210> SEQ ID NO 713
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<400> SEQUENCE: 713

auagauacac auucaacca                                            19


<210> SEQ ID NO 714
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uuuccagacu caaauagau                                            19
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<400> SEQUENCE: 715

uuaauugcug gacaaccgu 19

<210> SEQ ID NO 716
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uauuaauugc uggacaacc 19

<210> SEQ ID NO 717
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agucguucga gucaaugga 19

<210> SEQ ID NO 718
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guugcuggca gguccgugg 19

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<400> SEQUENCE: 719

cucaugaauu aga 13

<210> SEQ ID NO 720
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<400> SEQUENCE: 720

cugaggucaa uua 13

<210> SEQ ID NO 721
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gaggucaauu aaa 13

<210> SEQ ID NO 722
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ucugagguca auu 13

<210> SEQ ID NO 723
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ugaggucaau uaa 13

<210> SEQ ID NO 724
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uucugagguc aau 13

<210> SEQ ID NO 725
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gucagcugga uga 13

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uucugaugaa ucu 13

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uggacugagg uca 13

<210> SEQ ID NO 728

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gagucucacc auu 13

<210> SEQ ID NO 729
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gacugagguc aaa 13

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ucacagccau gaa 13

<210> SEQ ID NO 731
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agucucacca uuc 13

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aagcggaaag cca 13

<210> SEQ ID NO 733
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agcggaaagc caa 13

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accacaugga uga 13

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gccaugacca cau 13

<210> SEQ ID NO 736
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aagccaugac cac 13

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gcggaaagcc aau 13

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<212> TYPE: RNA
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<400> SEQUENCE: 738

aaauuucgua uuu 13

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auuucguauu ucu 13

<210> SEQ ID NO 740
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aaagccauga cca 13

<210> SEQ ID NO 741
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acauggauga uau 13

<210> SEQ ID NO 742
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gaaauuucgu auu 13

<210> SEQ ID NO 743
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<400> SEQUENCE: 743

gcgccuucug auu 13

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auuucucaug aau 13

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cucucaugaa uag 13

<210> SEQ ID NO 746
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aaguccaacg aaa 13

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augaugagag caa 13

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gcgaggaguu gaa 13

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ugauugauag uca 13

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agauagugca ucu 13

<210> SEQ ID NO 751
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auguguaucu auu 13

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uucuauagaa gaa 13

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uuguccagca auu 13

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acauggaaag cga 13

<210> SEQ ID NO 755
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gcaguccaga uua 13

<210> SEQ ID NO 756
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ugguugaaug ugu 13

<210> SEQ ID NO 757
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uuaugaaacg agu 13

<210> SEQ ID NO 758
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What is claimed is:

1. An isolated double stranded nucleic acid molecule comprising a guide strand and a passenger strand,

wherein the isolated double stranded nucleic acid molecule includes a double stranded region and a single stranded region, wherein the double stranded region is from 8-15 nucleotides long, wherein the single stranded region is at the 3' end of the guide strand and is 4-12 nucleotides long, wherein the single stranded region contains 3, 4, 5, 6, 7, 8, 9, 10, 11 or 12 phosphorothioate modifications, wherein at least 40% of the nucleotides of the isolated double stranded nucleic acid molecule are modified, and wherein the isolated double stranded nucleic acid molecule does not form a hairpin.

2. The isolated double stranded nucleic acid molecule of claim 1, wherein the double stranded region is 11, 12, 13, or 14 nucleotides long and/or wherein the single stranded region is at least 6 or at least 7 nucleotides long.

3. The isolated double stranded nucleic acid molecule of claim 1, wherein each nucleotide within the single stranded region has a phosphorothioate modification.

4. The isolated double stranded nucleic acid molecule of claim 1, wherein at least one of the nucleotides of the isolated double stranded nucleic acid molecule that is modified comprises a 2' O-methyl or a 2'-fluoro modification and/or wherein at least one of the nucleotides of the isolated double stranded nucleic acid molecule that is modified comprises a hydrophobic modification.

5. The isolated double stranded nucleic acid molecule of claim 1, wherein the guide strand of the double stranded nucleic acid molecule exhibits complementarity to a gene encoding for Osteopontin (SPP1), SOD1 or MAP4K4, optionally wherein the guide strand comprises SEQ ID NO:170, SEQ ID NO:40 or SEQ ID NO:25.

6. An isolated asymmetric nucleic acid molecule comprising:

a first polynucleotide wherein the first polynucleotide is complementary to a second polynucleotide and a target gene; and

a second polynucleotide,

wherein the second polynucleotide is at least 6 nucleotides shorter than the first polynucleotide, wherein the first polynucleotide includes a single stranded region of 6, 7, 8, 9, 10, 11 or 12 nucleotides, wherein the single stranded region of the first polynucleotide contains 3, 4, 5, 6, 7, 8, 9, 10, 11 or 12 phosphorothioate modifications, wherein the asymmetric nucleic acid molecule also includes a double stranded region of 8-15 nucleotides long, and wherein at least 50% of C and U nucleotides in the double stranded region are 2' O-methyl modified or 2'-fluoro modified.

7. The isolated asymmetric nucleic acid molecule of claim 6, wherein the single stranded region is 6 or 7 nucleotides long and/or wherein each nucleotide within the single stranded region has a phosphorothioate modification.

8. An isolated double stranded nucleic acid molecule comprising:

a guide strand of 17-21 nucleotides in length that has complementarity to a target gene, and a passenger strand of 8-16 nucleotides in length,

wherein the isolated double stranded nucleic acid molecule includes a double stranded region of 8-15 nucleotides long and a single stranded region, wherein the guide strand and the passenger strand form the double stranded nucleic acid molecule having the double stranded region and the single stranded region, wherein the single stranded region is at the 3' end of the guide strand and is 4-12 nucleotides in length, wherein the single stranded region comprises 2-12 phosphorothioate modifications, wherein at least 40% of the nucleotides of the isolated double stranded nucleic acid molecule are modified, and wherein the isolated double stranded nucleic acid molecule does not form a hairpin.

9. The isolated double stranded nucleic acid molecule of claim 8, wherein the isolated double stranded nucleic acid molecule contains at least one hydrophobic base modification and wherein the hydrophobic base modification comprises a hydrophobic modification of a pyrimidine base, optionally at position 4 or 5, optionally wherein the hydrophobic base modification is selected from the group consisting of a phenyl, 4-pyridyl, 2-pyridyl, indolyl, isobutyl, tryptophanyl ($C_8H_6N)CH_2CH(NH_2)CO$), methyl, butyl, aminobenzyl, and naphthyl modification of a uridine or cytidine.

10. A method for inhibiting the expression of a target gene in a mammalian cell, comprising contacting the mammalian cell with an isolated double stranded nucleic acid molecule comprising a guide strand and a passenger strand,

wherein the isolated double stranded nucleic acid molecule includes a double stranded region and a single stranded region, wherein the double stranded region is from 8-15 nucleotides long, wherein the single stranded region is at the 3' end of the guide strand and is 4-12 nucleotides long, wherein the single stranded region of the guide strand contains 3, 4, 5, 6, 7, 8, 9, 10, 11 or 12 phosphorothioate modifications, wherein at least 40% of the nucleotides of the isolated double stranded nucleic acid molecule are modified, and wherein the isolated double stranded nucleic acid molecule does not form a hairpin.

11. The method of claim **10**, wherein the double stranded region is 11, 12, 13, or 14 nucleotides long and/or wherein the single stranded region is at least 6 or at least 7 nucleotides long.

12. The method of claim **10**, wherein each nucleotide within the single stranded region has a phosphorothioate modification.

13. The method of claim **10**, wherein at least one of the nucleotides of the isolated double stranded nucleic acid molecule that is modified comprises a 2' O-methyl or a 2'-fluoro modification and/or wherein at least one of the nucleotides of the isolated double stranded nucleic acid molecule that is modified comprises a hydrophobic modification.

14. The method of claim **10**, wherein the double stranded nucleic acid molecule exhibits complementarity to a gene encoding for Osteopontin (SPP1), SOD1 or MAP4K4, optionally wherein the guide strand comprises SEQ ID NO:170, SEQ ID NO:40 or SEQ ID NO:25.

15. The isolated double stranded nucleic acid molecule of claim **1**, wherein the

double stranded nucleic acid molecule is non-covalently complexed to a hydrophobic molecule, wherein the hydrophobic molecule is a polycationic molecule.

16. The isolated double stranded nucleic acid molecule of claim **15**, wherein the polycationic molecule is selected from the group consisting of protamine, arginine rich peptides, and spermine.

17. The isolated double stranded nucleic acid molecule eof claim **1**, wherein the double stranded nucleic acid molecule is double stranded RNA, directly complexed to a hydrophobic molecule without a linker, wherein the hydrophobic molecule is not cholesterol.

* * * * *